

Gastrointestinal Tract Infections

20

Introduction

Ingested pathogens may cause disease confined to the gut or involving other parts of the body

Ingestion of pathogens can cause many different infections. These may be confined to the gastrointestinal tract or initiated in the gut before spreading to other parts of the body. In this chapter we consider the important bacterial causes of diarrheal disease and summarize the other bacterial causes of food-associated infection and food poisoning. Viral and parasitic causes of diarrheal disease are discussed, as well as infections acquired via the gastrointestinal tract and causing disease in other body systems, including typhoid and paratyphoid fevers, listeriosis, and some forms of viral hepatitis. For clarity, all types of viral hepatitis are included in this chapter. Infections of the liver can also result in liver abscesses, and several parasitic infections cause liver disease. Peritonitis and intra-abdominal abscesses can arise from seeding of the abdominal cavity by organisms from the gastrointestinal tract. Several different terms are used to describe infections of the gastrointestinal tract; those in common use are shown in *Figure 20.1*.

A wide range of microbial pathogens is capable of infecting the gastrointestinal tract and the important bacterial and viral pathogens are listed in *Figure 20.2*. They are acquired by the fecal–oral route, from fecally-contaminated food, fluids or fingers.

For an infection to occur, the pathogen must be ingested in sufficient numbers or possess attributes to elude the host defenses of the upper gastrointestinal tract and reach the intestine (*Fig. 20.3*; see also Chapter 7). Here they remain localized and cause disease as a result of multiplication and/or toxin production, or they may invade through the intestinal mucosa to reach the lymphatics or the bloodstream (*Fig. 20.4*). The damaging effects resulting from infection of the gastrointestinal tract are summarized in *Figure 20.5*.

Food-associated infection versus food poisoning

Infection associated with consumption of contaminated food is often termed ‘food poisoning’, but ‘food-associated infection’ is a better term. True food poisoning occurs after consumption of food containing toxins, which may be chemical (e.g. heavy metals) or bacterial in origin (e.g. from *Clostridium botulinum* or *Staphylococcus aureus*). The bacteria multiply and produce toxin within contaminated food. The organisms may be destroyed during food preparation, but the toxin is unaffected, consumed and acts within hours. In food-associated infections, the food may simply act as a vehicle for the pathogen (e.g. *Campylobacter*) or provide conditions in which the pathogen can multiply to produce numbers large enough to cause disease (e.g. *Salmonella*).

Diarrheal Diseases

Diarrhea is the most common outcome of gastrointestinal tract infection

Infections of the gastrointestinal tract range in their effects from a mild self-limiting attack of ‘the runs’ to severe, sometimes fatal, diarrhea. There may be associated vomiting, fever and malaise. Diarrhea is the result of an increase in fluid and

TERMS USED TO DESCRIBE GASTROINTESTINAL TRACT INFECTIONS
<p>gastroenteritis a syndrome characterized by gastrointestinal symptoms including nausea, vomiting, diarrhea and abdominal discomfort</p>
<p>diarrhea abnormal fecal discharge characterized by frequent and/or fluid stool; usually resulting from disease of the small intestine and involving increased fluid and electrolyte loss</p>
<p>dysentery an inflammatory disorder of the gastrointestinal tract often associated with blood and pus in the feces and accompanied by symptoms of pain, fever, abdominal cramps; usually resulting from disease of the large intestine</p>
<p>enterocolitis inflammation involving the mucosa of both the small and large intestine</p>

Fig. 20.1 As well as many colloquial expressions, several different clinical terms are used to describe infections of the gastrointestinal tract. Diarrhea without blood and pus is usually the result of enterotoxin production, whereas the presence of blood and/or pus cells in the feces indicates an invasive infection with mucosal destruction.

IMPORTANT BACTERIAL AND VIRAL PATHOGENS OF THE GASTROINTESTINAL TRACT			
pathogen	animal reservoir	foodborne	waterborne
Bacteria			
<i>Escherichia coli</i>	+?	+(EHEC)	+(ETEC)
<i>Salmonella</i>	+	+++	+
<i>Campylobacter</i>	+	+++	+
<i>Vibrio cholerae</i>	-	+	+++
<i>Shigella</i>	-	+	-
<i>Clostridium perfringens</i>	+	+++	-
<i>Bacillus cereus</i>	-	++	-
<i>Vibrio parahaemolyticus</i>	-	++	-
<i>Yersinia enterocolitica</i>	+	+	-
Viruses			
rotavirus	-	-	-
small round viruses	-	++	+

Fig. 20.2 Many different pathogens cause infections of the gastrointestinal tract. Some are found in both humans and animals while others are strictly human parasites. This difference has important implications for control and prevention. (EHEC, verotoxin-producing *Escherichia coli*; ETEC, enterotoxigenic *E. coli*.)

electrolyte loss into the gut lumen, leading to the production of unformed or liquid feces and can be thought of as the method by which the host forcibly expels the pathogen (and in doing so, aids its dissemination). However, diarrhea also occurs in many non-infectious conditions, and an infectious cause should not be assumed.

In the developing world, diarrheal disease is a major cause of mortality in children

In the developing world, diarrheal disease is a major cause of morbidity and mortality, particularly in young children. In the developed world it remains a very common complaint, but is usually mild and self-limiting except in the very young, the elderly, and immunocompromised patients. Most of the pathogens listed in *Figure 20.2* are found throughout the world, but some such as *Vibrio cholerae*, have a more limited geographic distribution. However, such infections can be acquired by travellers to these areas and imported into their home countries.

Many cases of diarrheal disease are not diagnosed, either because they are mild and self-limiting and the patient does not seek medical attention, or because medical and laboratory facilities are unavailable, particularly in developing countries. It is generally impossible to distinguish on clinical

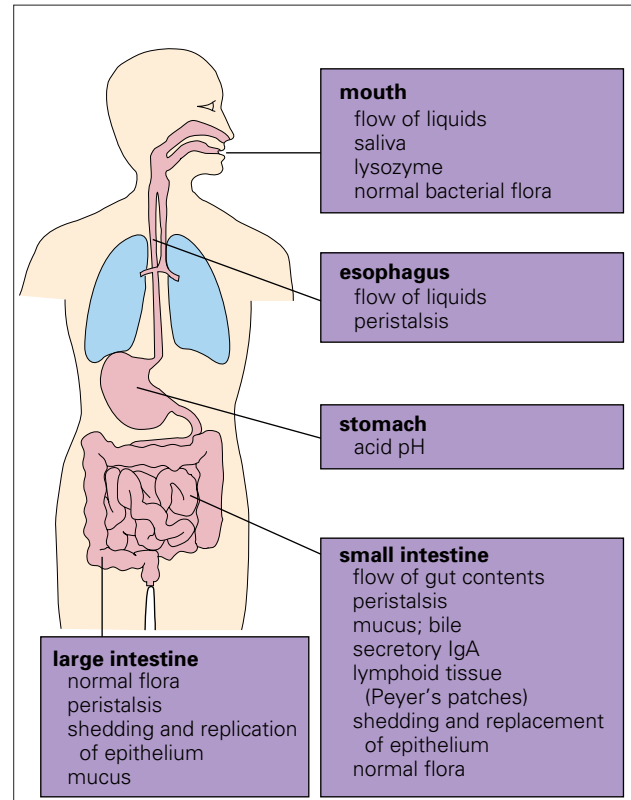


Fig. 20.3 Every day we swallow large numbers of microorganisms. Because of the body's defense mechanisms, however, they rarely succeed in surviving the passage to the intestine in sufficient numbers to cause infection.

grounds between infections caused by the different pathogens. However, information about the patient's recent food and travel history, and macroscopic and microscopic examination of the feces for blood and pus can provide helpful clues. A precise diagnosis can only be achieved by laboratory investigations. This is especially important in outbreaks, because of the need to instigate appropriate epidemiologic investigations and control measures.

Bacterial causes of diarrhea

Escherichia coli

This is one of the most versatile of all bacterial pathogens. Some strains are important members of the normal gut flora in man and animals (see Chapter 3), whereas others possess virulence factors that enable them to cause infections in the intestinal tract or at other sites, particularly the urinary tract (see Chapter 18). Strains that cause diarrheal disease do so by several distinct pathogenic mechanisms and differ in their epidemiology (*Fig. 20.6*).

There are four distinct groups of E. coli with different pathogenetic mechanisms

Enterotoxigenic *Escherichia coli* (ETEC) (*Fig. 20.6*) possess colonization factors, which bind the bacteria to specific receptors

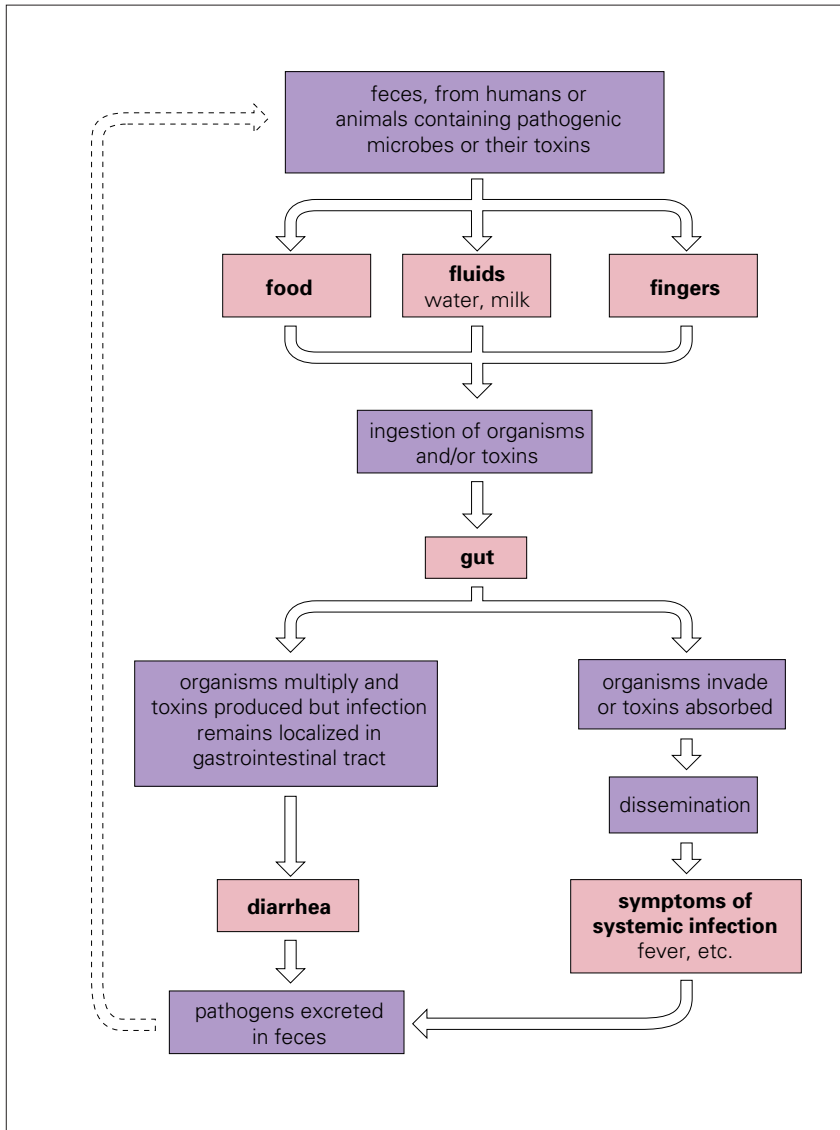


Fig. 20.4 Infections of the gastrointestinal tract can be grouped into those that remain localized in the gut and those that invade beyond the gut to cause infection in other sites in the body. In order to spread to a new host, pathogens are excreted in large numbers in the feces and must survive in the environment for long enough to infect another person directly or indirectly through contaminated food or fluids.

DAMAGE RESULTING FROM INFECTION OF THE GASTROINTESTINAL TRACT
pharmacologic action of bacterial toxins, local or distant to site of infection e.g. cholera, staphylococcal food poisoning
local inflammation in response to superficial microbial invasion e.g. shigellosis, amebiasis
deep invasion to blood or lymphatics dissemination to other body sites e.g. hepatitis A, enteric fevers
perforation of mucosal epithelium after infection, surgery or accidental trauma e.g. peritonitis, intra-abdominal abscesses

Fig. 20.5 Infection of the gastrointestinal tract can cause damage locally or at distant sites.

on the intestinal cell membrane (*Fig. 20.7*) where the organisms produce powerful enterotoxins:

- Heat-labile enterotoxin (LT) is very similar in structure and mode of action to cholera toxin produced by *V. cholerae*, and infections with strains producing LT can mimic cholera, particularly in young and malnourished children.
- Other ETEC strains produce heat-stable enterotoxins (STs) in addition to or instead of LT. STs have a similar but distinct mode of action to that of LT. ST_A activates guanylate cyclase activity causing an increase in cyclic guanosine monophosphate, which results in increased fluid secretion. The mechanism of action of ST_B is unknown. Unlike LT, the STs are not immunogenic and cannot therefore be detected by immunologic tests (*Fig. 20.6*).

Other *E. coli* strains produce a verotoxin, so-called because it is toxic to tissue cultures of 'vero' cells. After attachment to the intestinal mucosa (by an 'attaching-effacing' mechanism), the organisms elaborate verotoxin, which has a direct effect on

CHARACTERISTICS OF <i>ESCHERICHIA COLI</i> STRAINS CAUSING GASTROINTESTINAL INFECTIONS		
pathogenic group	epidemiology	laboratory diagnosis*
enterotoxigenic <i>E. coli</i> (ETEC)	<p>most important bacterial cause of diarrhea in children in developing countries</p> <p>most common cause of travellers' diarrhea</p> <p>water contaminated by human or animal sewage may be important in spread</p>	<p>isolate organisms from feces</p> <p>test for production of LT (but not ST) by immunologic techniques e.g. ELISA</p> <p><i>test for production of STs by detecting accumulation of fluid in ligated ileal loops of experimental animals (not in routine use)</i></p> <p><i>gene probes specific for LT and ST genes available for detection of ETEC in feces and in food and water samples</i></p>
enteroinvasive <i>E. coli</i> (EIEC)	<p>important cause of diarrhea in areas of poor hygiene</p> <p>infections usually foodborne; no evidence of animal or environmental reservoir</p>	<p>isolate organisms from feces;</p> <p><i>test for enteroinvasive potential in tissue culture cells</i></p>
verotoxin-producing <i>E. coli</i> (EHEC)	<p>serotype O157 most important EHEC in human infections</p> <p>outbreaks and sporadic cases occur worldwide</p> <p>food and unpasteurized milk important in spread</p>	<p>isolate organisms from feces</p> <p>proportion of EHEC in fecal sample may be very low (often <1% of <i>E. coli</i> colonies)</p> <p>usually sorbitol non-fermenters</p> <p><i>EHEC-producing colonies can be identified with DNA probes in colony hybridization tests</i></p>
enteropathogenic <i>E. coli</i> (EPEC)	<p>EPEC strains belong to particular O serotypes</p> <p>cause sporadic cases and outbreaks of infection in babies and young children</p> <p>importance in adults not known</p>	<p>isolate organisms from feces</p> <p>determine serotype of several colonies with polyvalent antisera for known EPEC types</p> <p><i>adhesion to tissue culture cells can be demonstrated by a fluorescence actin staining test</i></p>

Fig. 20.6 *Escherichia coli* is a major cause of gastrointestinal infection, particularly in developing countries and in travellers. There is a range of pathogenic mechanisms within the species,

resulting in more or less invasive disease. *Specialized tests are given in italics. (ELISA, enzyme-linked immunosorbent assay; LT, heat-labile enterotoxin; ST, heat-stable enterotoxin.)

intestinal epithelium resulting in diarrhea. These strains are referred to as verotoxin-producing *E. coli* (EHEC) (Fig. 20.6) because they cause hemorrhagic colitis (HC) and hemolytic-uremic syndrome (HUS). In HC there is destruction of the mucosa and consequent hemorrhage; this may be followed by HUS. Verotoxin receptors have been identified on renal epithelium and may account for the kidney involvement.

Enteropathogenic *E. coli* (EPEC) were the first group of *E. coli* intestinal pathogens to be described, but their mechanism of pathogenicity remains unclear. They do not appear to produce any toxins, but have a particular mechanism of adhesion ('attaching-effacing' as with EHEC) to enterocytes that appears to destroy the microvilli (Fig. 20.8).

Enteroinvasive *E. coli* (EIEC) attach specifically to the mucosa of the large intestine and invade the cells by being taken in by endocytosis. Inside the cell they lyse the endo-

cytic vacuole, multiply and spread to adjacent cells, causing tissue destruction and consequently inflammation.

ETEC is the most important bacterial cause of diarrhea in children in developing countries

The diarrhea produced by *E. coli* varies from mild to severe depending upon the strain and the underlying health of the host. ETEC diarrhea in children in developing countries may be clinically indistinguishable from cholera. EIEC and EHEC strains both cause bloody diarrhea. Following EHEC infection, HUS is characterized by acute renal failure (Fig. 20.9), anemia and thrombocytopenia, and there may be neurologic complications. HUS is the most common cause of acute renal failure in children in the UK and USA.

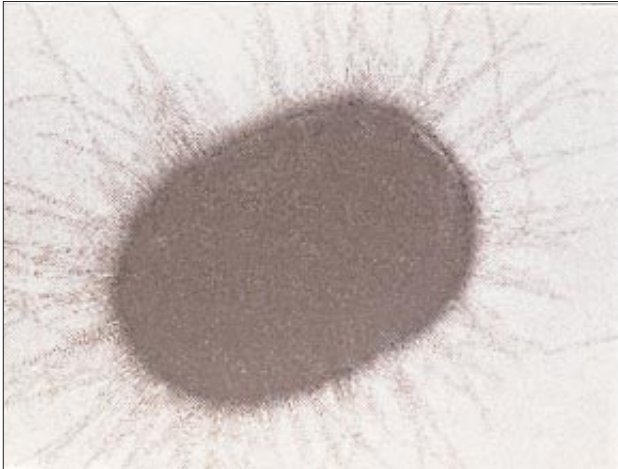


Fig. 20.7 Electron micrograph of enterotoxin *Escherichia coli*, showing pili necessary for adherence to mucosal epithelial cells. (Courtesy of S Knutton.)

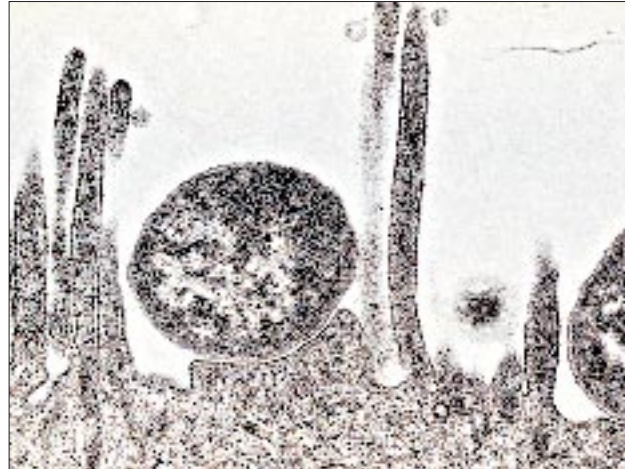


Fig. 20.8 Electron micrograph of enteropathogenic *Escherichia coli* adhering to the brush border of intestinal mucosal cells with localized destruction of microvilli. (Courtesy of S Knutton.)

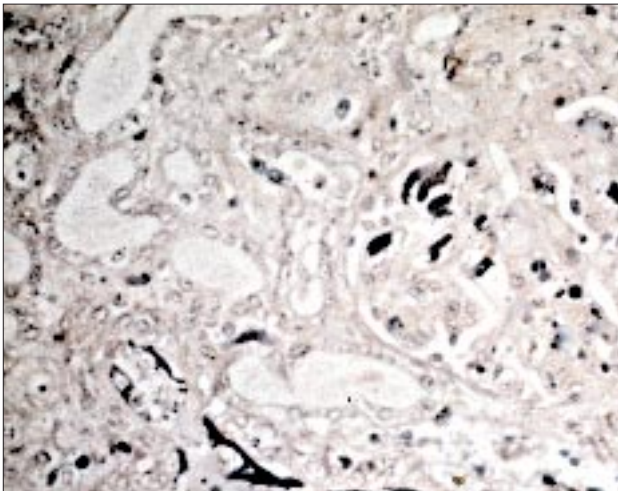


Fig. 20.9 Verotoxin-producing *Escherichia coli* infection, showing fibrin 'thrombi' in glomerular capillaries in hemolytic-uremic syndrome. Weigert stain. (Courtesy of HR Powell.)

Specific tests are needed to identify strains of pathogenic *E. coli*

Because *E. coli* is a member of the normal gastrointestinal flora, specific tests are required to identify strains that may be responsible for diarrheal disease. These are summarized in *Figure 20.6*. Infections are more common in children and are often travel-associated, and these factors should be considered when samples are received in the laboratory.

Antibacterial therapy is not indicated for *E. coli* diarrhea

Specific antibacterial therapy is not indicated. Fluid replacement may be necessary, especially in young children. Treatment of HUS is urgent and may involve dialysis.

Provision of a clean water supply and adequate systems for sewage disposal are fundamental to the prevention of

diarrheal disease. Food and unpasteurized milk can be important vehicles of infection, especially for EIEC and EHEC, but there is no evidence of an animal or environmental reservoir.

Salmonella

Salmonellae are the most common cause of food-associated diarrhea in many developed countries

Until recently salmonellae were the most common cause of food-associated diarrhea in the developed world, but in some countries they have now been beaten into second place by campylobacter. Like *E. coli*, the salmonellae belong to the Enterobacteria and the genus *Salmonella* has been divided into more than 2000 species on the basis of differences in the cell wall (O) and flagellar (H) antigens (Kauffmann–White scheme). However, more recent studies indicate that there is a single species, or at most three species, and that serotypes should not be given species status (see Appendix). Nevertheless it is useful to be able to distinguish between serotypes for epidemiologic purposes, for example when tracing the source of an outbreak.

All salmonellae except for *Salmonella typhi* and *S. paratyphi* are found in animals as well as humans. There is a large animal reservoir of infection, which is transmitted to man via contaminated food, especially poultry and dairy products (*Fig. 20.10*). Waterborne infection is less frequent. Salmonella infection is also transmitted from person to person and therefore secondary spread can occur, for example within a family after one member has become infected after consuming contaminated food.

Diarrhea is the most common manifestation of infection caused by Salmonella spp. other than *S. typhi* and *S. paratyphi*

Diarrhea is produced as a result of invasion by the salmonellae of epithelial cells in the terminal portion of the small intestine (*Fig. 20.11*). Initial entry is probably through uptake by M cells (the 'antigenic samplers' of the bowel) with

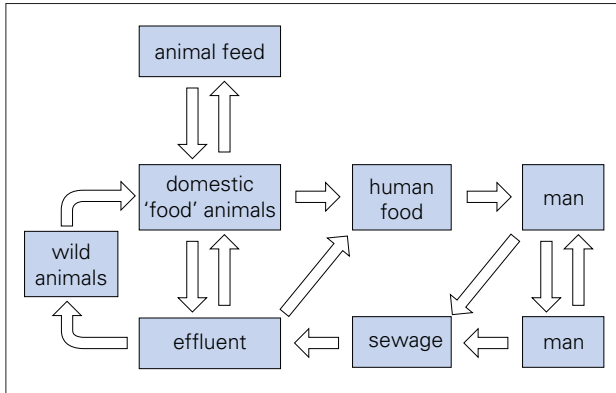


Fig. 20.10 The recycling of salmonellae. With the exception of *Salmonella typhi*, salmonellae are widely distributed in animals, providing a constant source of infection for man. Excretion of large numbers of salmonellae from infected individuals and carriers allows the organisms to be 'recycled'.

subsequent spread to epithelial cells. A similar route of invasion occurs in *Shigella*, *Yersinia* and reovirus infections. The bacteria migrate to the lamina propria layer of the ileocecal region, where their multiplication stimulates an inflammatory response, which both confines the infection to the gastrointestinal tract and mediates the release of prostaglandins. These in turn activate cyclic adenosine monophosphate (cAMP) and fluid secretion, resulting in diarrhea. Salmonellae do not appear to produce enterotoxins.

Species of *Salmonella* that normally cause diarrhea (e.g. *S. enteritidis*, *S. cholerae suis*) may become invasive in patients with particular predispositions (e.g. children and patients with cancer or sickle cell anemia). The organisms are not contained within the gastrointestinal tract, but invade the body to cause septicemia; consequently, many organs become seeded with salmonellae, sometimes leading to osteomyelitis, pneumonia or meningitis.

In the vast majority of cases, *Salmonella* spp. cause an acute but self-limiting diarrhea, though in the young and the elderly the symptoms may be more severe. Vomiting is rare and fever is usually a sign of invasive disease (Fig. 20.12). In the UK there is a reported annual incidence of salmonella bacteremia of approximately 150 cases, with about 70 deaths. This should be set in context against the approximately 30 000 reported cases of diarrhea.

S. typhi and *S. paratyphi* invade the body from the gastrointestinal tract to cause systemic illness and are discussed in a later section.

Salmonella diarrhea can be diagnosed by culture on selective media

The methods for culturing fecal specimens on selective media are summarized in the Appendix. The organisms are not fastidious and can usually be isolated within 24 hours, although small numbers may require enrichment in selenite broth before culture. Preliminary identification can be made rapidly, but the complete result, including serotype, takes at least 48 hours.

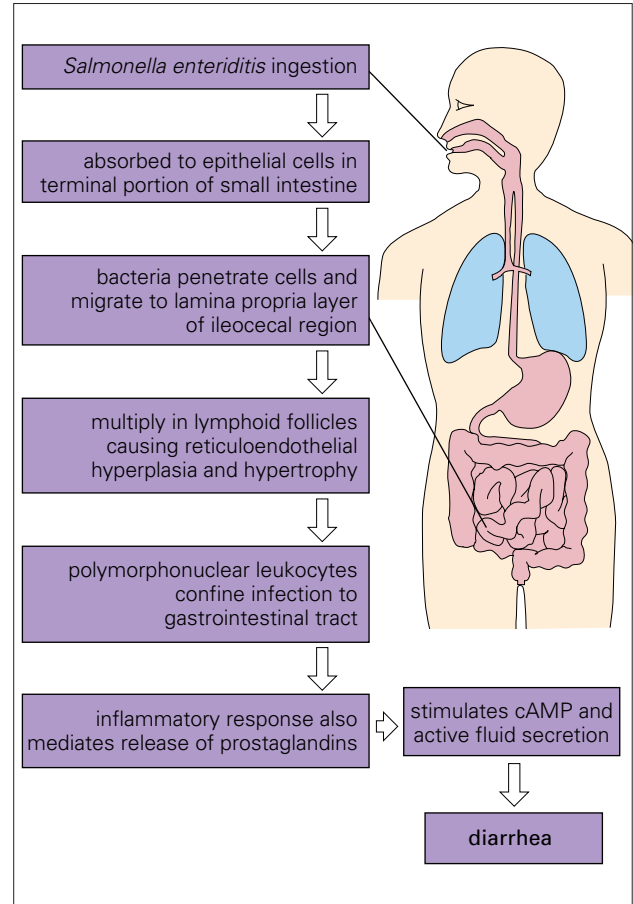


Fig. 20.11 The passage of salmonellae through the body to the gut. The vast majority of salmonellae cause infection localized to the gastrointestinal tract and do not invade beyond the gut mucosa. They do not produce enterotoxins. (cAMP, cyclic adenosine monophosphate.)

Fluid and electrolyte replacement may be needed for salmonella diarrhea

Diarrhea is usually self-limiting and resolves without treatment. Fluid and electrolyte replacement may be required, particularly in the very young and the elderly. Unless there is evidence of invasion and septicemia, antibiotics should be positively discouraged because they do not reduce the symptoms or shorten the illness, and may prolong excretion of salmonellae in the feces. There is some evidence that symptomatic treatment with drugs that reduce diarrhea has the same adverse effect.

Salmonellae may be excreted in the feces for several weeks after a salmonella infection

Figure 20.10 illustrates the problems associated with the prevention of salmonella infections. The large animal reservoir makes it impossible to eliminate the organisms and therefore preventive measures must be aimed at 'breaking the chain' between animal and man, and person to person. Such measures include:

CLINICAL FEATURES OF BACTERIAL DIARRHEAL DISEASE						
pathogen	incubation period	duration	symptoms			
			diarrhea	vomiting	abdominal cramps	fever
<i>Salmonella</i>	6h–2 days	48h–7 days	++	+	–	+
<i>Campylobacter</i>	2–11 days	3 days–3 weeks	+++	–	++	++
<i>Shigella</i>	1–4 days	2–3 days	++/+++	–	+	+
<i>Vibrio cholerae</i>	2–3 days	up to 7 days	++++	+	–	–
<i>Vibrio parahaemolyticus</i>	8h–2 days	3 days	+/++	+	+	+
<i>Clostridium perfringens</i>	8h–1 day	12h–1 day	++	–	++	–
<i>Bacillus cereus</i> diarrheal emetic	8h–12h 15min–4h	12h–1 day 12h–2 days	++ +	– ++	++	–
<i>Yersinia enterocolitica</i>	4–7 days	1–2 weeks	++	–	++	+

Fig. 20.12 The clinical features of bacterial diarrhea infection. It is difficult, if not impossible, to determine the likely cause of a diarrheal illness on the basis of clinical features alone, and laboratory investigations are essential to identify the pathogen.

- Maintaining adequate standards of public health (clean drinking water and proper sewage disposal).
- Education programs on hygienic food preparation.

Following an episode of salmonella diarrhea, an individual can continue to carry and excrete organisms in the feces for several weeks. Although in the absence of symptoms the organisms will not be dispersed so liberally into the environment, thorough handwashing before food handling is essential. People employed as food handlers are excluded from work until three specimens of feces have failed to grow salmonella.

Campylobacter

Campylobacters are among the commonest causes of diarrhea

Campylobacter spp. are curved or S-shaped Gram-negative rods (Fig. 20.13). They have long been known to cause diarrheal disease in animals, but are also one of the most common causes of diarrhea in humans. The delay in recognizing the importance of these organisms was due to their cultural requirements, which differ from those of the Enterobacteria as they are microaerophilic and thermophilic; they do not therefore grow on the media used for isolating *E. coli* and salmonellae. Several species of the genus *Campylobacter* are associated with human disease, but *Campylobacter jejuni* is by far the most common. *Campylobacter pylori*, now classified as *Helicobacter pylori* is an important cause of gastritis and gastric ulcers.

As with salmonellae, there is a large animal reservoir of campylobacter in cattle, sheep, rodents, poultry and wild birds. Infections are acquired by consumption of contaminated food, especially poultry, milk or water. Recent studies have shown an association between infection and consumption of milk from bottles with tops that have been

pecked by wild birds. Household pets such as dogs and cats can become infected and provide a source for human infection, particularly for young children. Person to person spread by the fecal–oral route is rare, as is transmission from food handlers.

Campylobacter diarrhea is clinically indistinguishable from that of salmonella diarrhea

The pathogenesis of campylobacter diarrhea has not yet been elucidated. The gross pathology and histologic appearances of ulceration and inflamed bleeding mucosal surfaces in the jejunum, ileum and colon (Fig. 20.14) are compatible with invasion of the bacteria, but the production of cytotoxins by *C. jejuni* has also been demonstrated. Invasion and bacteremia are not uncommon, particularly in neonates and debilitated adults.



Fig. 20.13 *Campylobacter jejuni* infection. Gram stain showing Gram-negative, S-shaped bacilli. (Courtesy of I Farrell.)

The clinical presentation is indistinguishable from diarrhea caused by salmonellae although the disease may have a longer incubation period and a longer duration. The key features are summarized in *Figure 20.12*.

Cultures for campylobacter should be set up routinely in every investigation of a diarrheal illness

The methods are described in the Appendix, but it is important to note that the media and conditions for growth differ from those required for the Enterobacteria. Growth is often somewhat slow compared with that of the Enterobacteria, but a presumptive identification should be available within 48 hours of culture.

Erythromycin is used for severe campylobacter diarrhea

Erythromycin is the antibiotic of choice for cases of diarrheal disease that are severe enough to warrant treatment. Invasive infections may require treatment with an aminoglycoside.

The preventive measures for salmonella infections described above are equally applicable to the prevention of campylobacter infections, but there are no requirements for the screening of food handlers because contamination of food by this route is very uncommon.

Cholera

Cholera is an acute infection of the gastrointestinal tract caused by the comma-shaped Gram-negative bacterium *V. cholerae* (*Fig. 20.15*). The disease has a long history characterized by epidemics and pandemics. The last cases of cholera acquired in the UK were in the last century following the introduction of the bacterium by sailors arriving from Europe, and in 1849 Snow published his historic essay *On the Mode of Communication of Cholera*.

Cholera flourishes in communities with inadequate clean drinking water and sewage disposal

The 1990s have witnessed the seventh pandemic of cholera spreading into Latin America, and the disease remains endemic in South East Asia and parts of Africa and South America. Unlike salmonellae and campylobacter, *V. cholerae* is a free-living inhabitant of fresh water, but causes infection only in humans. Asymptomatic human carriers are believed to be a major reservoir. The disease is spread via contaminated food; shellfish grown in fresh and estuarine waters have also been implicated. Direct person to person spread is thought to be uncommon. Therefore cholera continues to flourish in communities where there is absent or unreliable provision of clean drinking water and sewage disposal. Cases still occur in developed countries, but high standards of hygiene mean that secondary spread should not occur. Over the past 20 years there have been 66 cases reported in the UK and 10 cases in the USA, which amounts to about one case for every 500 000 travellers to areas with endemic cholera.

***V. cholerae* serotypes are based on somatic (O) antigens**

Serotype O1 is the most important and is further divided into two biotypes: classical and El Tor (*Fig. 20.16*). The El Tor biotype, named after the quarantine camp where it was first isolated from pilgrims returning from Mecca, differs from classical *V. cholerae* in several ways. In particular it causes only a mild diarrhea and has a higher ratio of carriers to cases than classical cholera; carriage is also more prolonged and the organisms survive better in the environment. The El Tor biotype, which was responsible for the seventh pandemic, has now spread throughout the world and has largely displaced the classical biotype.

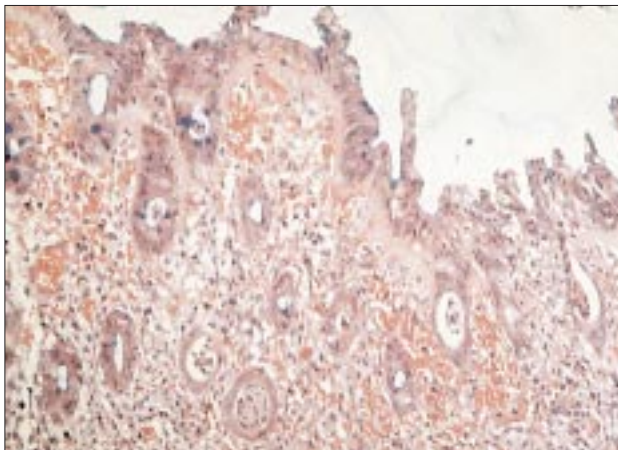


Fig. 20.14 Inflammatory enteritis caused by *Campylobacter jejuni*, involving the entire mucosa, with flattened atrophic villi, necrotic debris in the crypts and thickening of the basement membrane. Cresyl-fast violet stain. (Courtesy of J Newman.)



Fig. 20.15 Scanning electron micrograph of *Vibrio cholerae* showing comma-shaped rods with a single polar flagellum. $\times 13\,000$. (Courtesy of DK Banerjee.)

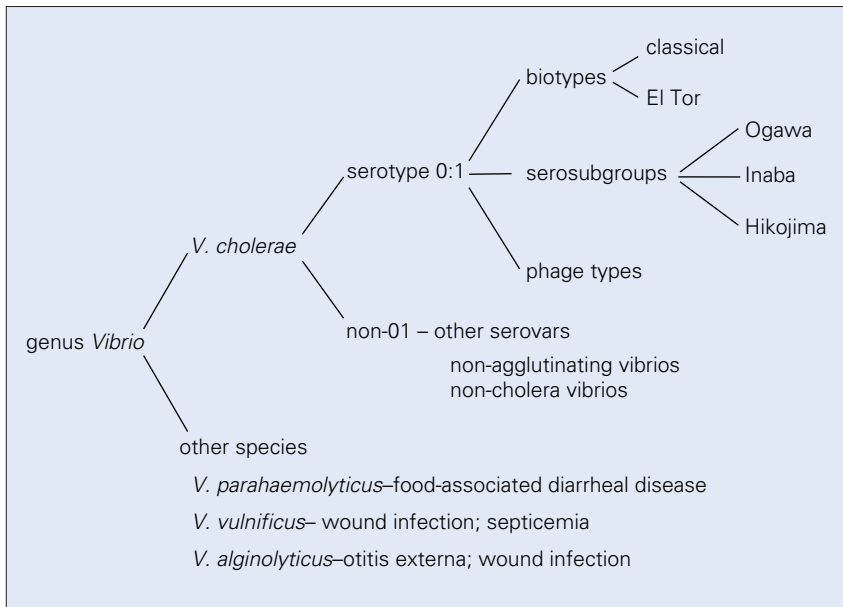


Fig. 20.16 *Vibrio cholerae* serotype O:1, the cause of cholera, can be subdivided into different biotypes with different epidemiologic features, and into serosubgroups and phage types for the purposes of investigating outbreaks of infection. Although *V. cholerae* is the most important pathogen of the genus, other species can also cause infections of both the gastrointestinal tract and other sites.

In 1992 a new non-O1 strain (O139) arose in south India and spread rapidly. It is able to infect O1-immune individuals and cause epidemics, and has been proclaimed as the eighth pandemic strain of cholera. *V. cholerae* O139 appears to have originated from the El Tor O1 biotype when the latter acquired a new O (capsular) antigen by horizontal gene transfer from a non-O1 strain. This provided the recipient strain with a selective advantage in a region where a large part of the population is immune to O1 strains.

Other species of *Vibrio* cause a variety of infections in man (Fig. 20.16). *V. parahaemolyticus* is another cause of diarrheal disease, but this is usually much less severe than cholera (see below).

The symptoms of cholera are caused by an enterotoxin

The symptoms of cholera are entirely due to the production of an enterotoxin in the gastrointestinal tract (see Chapter 12). However, the organism requires additional virulence factors to enable it to survive the host defenses and adhere to the intestinal mucosa. These are illustrated in Figure 20.17 (see also Chapter 8).

The clinical features of cholera are summarized in Figure 20.12. The severe watery non-bloody diarrhea is known as rice water stool because of its appearance (Fig. 20.18) and can result in the loss of one liter of fluid every hour. It is this fluid loss and the consequent electrolyte imbalance that results in marked dehydration, metabolic acidosis (loss of bicarbonate), hypokalemia (potassium loss) and hypovolemic shock resulting in cardiac failure. Untreated, the mortality from cholera is 40–60%; rapidly instituted fluid and electrolyte replacement reduces the mortality to less than 1%.

Culture is necessary to diagnose sporadic or imported cases of cholera and carriers

In countries where cholera is prevalent, diagnosis is based on

clinical grounds and laboratory confirmation is rarely sought. It is worth remembering that ETEC infection can resemble cholera in its severity, but for both diseases, fluid and electrolyte replacement are of paramount importance. The methods are given in the Appendix.

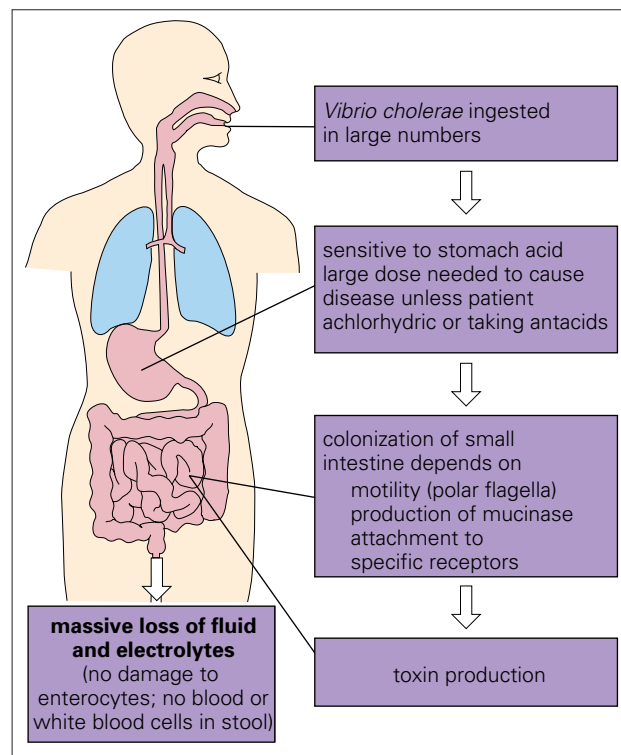


Fig. 20.17 The production of an enterotoxin is central to the pathogenesis of cholera, but the organisms must possess other virulence factors to allow them to reach the small intestine and to adhere to the mucosal cells.



Fig. 20.18 Rice water stool in cholera. (Courtesy of AM Geddes.)

Prompt rehydration with fluids and electrolytes is central to the treatment of cholera

Oral or intravenous rehydration may be used. Antibiotics are not necessary, but tetracycline may be given as some evidence indicates that this reduces the time of excretion of *V. cholerae* thereby reducing the risk of transmission. There have, however, been reports of tetracycline-resistant *V. cholerae* in some areas.

As with other diarrheal disease, a clean drinking water supply and adequate sewage disposal are fundamental to the prevention of cholera. As there is no animal reservoir, it should in theory be possible to eliminate the disease. However, carriage in humans, albeit for only a few weeks, occurs in 1–20% of previously infected patients making eradication difficult to achieve.

Killed whole-cell cholera vaccine is no longer recommended by the WHO

A killed whole-cell vaccine is available and is given parenterally, but is effective in only about 50% of those vaccinated, with protection lasting for only 3–6 months. It is no longer recommended by the World Health Organization (WHO) for travellers to cholera-endemic areas, although it may be required in certain countries. Field trials of various oral vaccines are in progress.

Shigellosis

Symptoms of *Shigella* infection range from mild to severe depending upon the infecting species

Shigellosis is also known as bacillary dysentery (in contrast to amebic dysentery; see below) because in its more severe form it is characterized by an invasive infection of the mucosa of the large intestine causing inflammation and resulting in the presence of pus and blood in the diarrheal stool. However, symptoms range from mild to severe depending upon the species of *Shigella* involved and on the underlying state of health of the host. There are four species:

- *Shigella sonnei* causes most infections at the mild end of the spectrum.
- *Shigella flexneri* and *S. boydii* usually produce more severe disease.
- *Shigella dysenteriae* is the most serious.

Shigellosis is primarily a pediatric disease. When associated with severe malnutrition it may precipitate complications such as the protein deficiency syndrome ‘kwashiorkor’. Like *V. cholerae*, shigellae are human pathogens without an animal reservoir, but unlike the vibrios, they are not found in the environment, being spread from person to person by the fecal–oral route and less frequently by contaminated food and water. Shigellae appear to be able to initiate infection from a small infective dose (10–100 organisms) and therefore spread is easy in situations where sanitation or personal hygiene may be poor (e.g. refugee camps, nurseries, day care centers and institutions for the handicapped).

***Shigella* diarrhea is usually watery at first, but later contains mucus and blood**

Shigellae attach to, and invade, the mucosal epithelium of the distal ileum and colon, causing inflammation and ulceration (Fig. 20.19). However, they rarely invade through the gut wall to the bloodstream. Enterotoxin is produced, but its role in pathogenesis is uncertain since toxin-negative mutants still produce disease.

The main features of shigella infection are summarized in Figure 20.12. Diarrhea is usually watery at first, but later contains mucus and blood. Lower abdominal cramps can be severe. The disease is usually self-limiting, but dehydration can occur, especially in the young and elderly. Complications can be associated with malnutrition (see above).

Antibiotics should only be given for severe shigella diarrhea

Rehydration may be indicated. Antibiotics should not be given except in severe cases. Plasmid-mediated resistance is

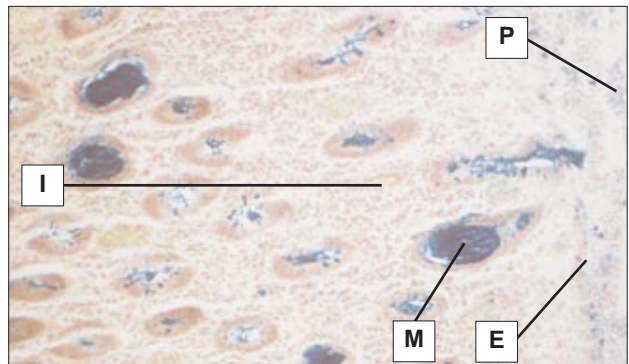


Fig. 20.19 Shigellosis. Histology of the colon showing disrupted epithelium covered by pseudomembrane and interstitial infiltration. Mucin glands have discharged their contents and the goblet cells are empty. Colloidal iron stain. (E, epithelium; I, interstitial infiltration; M, mucin in glands; P, pseudomembrane.) (Courtesy of RH Gilman.)

common and antibiotic susceptibility tests should be performed on shigella isolates if treatment is required.

Education in personal hygiene and proper sewage disposal are important. Cases may continue to excrete shigellae for a few weeks, but longer term carriage is unusual; therefore with adequate public health measures and no animal reservoir, the disease is potentially eradicable.

Other bacterial causes of diarrheal disease

The pathogens described in the previous sections are the major bacterial causes of diarrheal disease. Salmonella and campylobacter infections and some types of *E. coli* infections are most often food-associated, whereas cholera is more often waterborne and shigellosis is usually spread by direct fecal–oral contact. Other bacterial pathogens that cause food-associated infection or food poisoning are described below.

***V. parahaemolyticus* and *Yersinia enterocolitica* are foodborne Gram-negative causes of diarrhea**

V. parahaemolyticus is a halophilic (salt-loving) vibrio that contaminates seafood and fish. If these foods are consumed uncooked, diarrheal disease can result. The mechanism of pathogenesis is still unclear. Most strains associated with infection are hemolytic due to production of a heat-stable cytotoxin and have been shown to invade intestinal cells (in contrast to *V. cholerae*, which is non-invasive and cholera toxin, which is not cytotoxic).

The clinical features of infection are summarized in *Figure 20.12*. The methods used for the laboratory diagnosis of *V. parahaemolyticus* infection are given in the Appendix. As the special media for cultivating vibrios are not used routinely, the request form accompanying the specimen must provide adequate information about the patient's history and food consumption to indicate to the laboratory that vibrios should be looked for. Prevention of infection depends upon cooking fish and seafood properly.

Yersinia enterocolitica is a member of the Enterobacteriaceae and is a cause of food-associated infection, particularly in colder parts of the world. The reason for this geographic distribution is unknown, but it has been speculated that it is because the organism prefers to grow at temperatures of 22–25°C. *Y. enterocolitica* is found in a variety of animal hosts including rodents, rabbits, pigs, sheep, cattle, horses and domestic pets. Transmission to humans from household dogs has been reported. The organism survives and multiplies, albeit more slowly, at refrigeration temperatures (4°C) and has been implicated in outbreaks of infection associated with contaminated milk as well as other foods.

The mechanism of pathogenesis is unknown, but the clinical features of the disease result from invasion of the terminal ileum, necrosis in Peyer's patches and an associated inflammation of the mesenteric lymph nodes (*Fig. 20.20*). The presentation, with enterocolitis and often mesenteric adenitis, can easily be confused with acute appendicitis, particularly in children. The clinical features are summarized in *Figure 20.12*. The laboratory diagnosis is

outlined in the Appendix. As with *V. parahaemolyticus*, an indication of a suspicion of yersinia infection is useful so that the laboratory staff can process the specimen appropriately.

***Clostridium perfringens* and *Bacillus cereus* are spore-forming Gram-positive causes of diarrhea**

The Gram-negative organisms described in the previous sections invade the intestinal mucosa or produce enterotoxins, which cause diarrhea. None of these organisms produce spores. Two Gram-positive species are important causes of diarrheal disease, particularly in association with spore-contaminated food. These are *Clostridium perfringens* and *Bacillus cereus*.

Cl. perfringens is associated with diarrheal diseases in different circumstances and the pathogenesis is summarized in *Figure 20.21*:

- Enterotoxin-producing strains are a common cause of food-associated infection.
- Much more rarely β toxin-producing strains produce an acute necrotizing disease of the small intestine, accompanied by abdominal pain and diarrhea. This form occurs after the consumption of contaminated meat by people who are unaccustomed to a high protein diet and do not have sufficient intestinal trypsin to destroy the toxin. It is traditionally associated with the orgiastic pig feasts enjoyed by the natives of New Guinea, but also occurred in people released from prisoner of war camps.

The clinical features of the common type of infection are shown in *Figure 20.12*. The laboratory investigation of suspected *Cl. perfringens* infection is outlined in the Appendix. The organism is an anaerobe and grows readily on routine laboratory media. Enterotoxin production can be demonstrated by a latex agglutination method.



Fig. 20.20 *Yersinia enterocolitica* infection of the ileum, showing superficial necrosis of the mucosa and ulceration. (Courtesy of J Newman.)

Antibacterial treatment of *Cl. perfringens* diarrhea is rarely required. Prevention depends on thorough reheating of food before serving, or preferably avoiding cooking food too long before consumption.

Cl. perfringens is also an important cause of wound and soft tissue infections, as described in Chapter 23.

Bacillus cereus spores and vegetative cells contaminate many foods, and food-associated infection takes one of two forms:

- Diarrhea resulting from the production of enterotoxin in the gut.

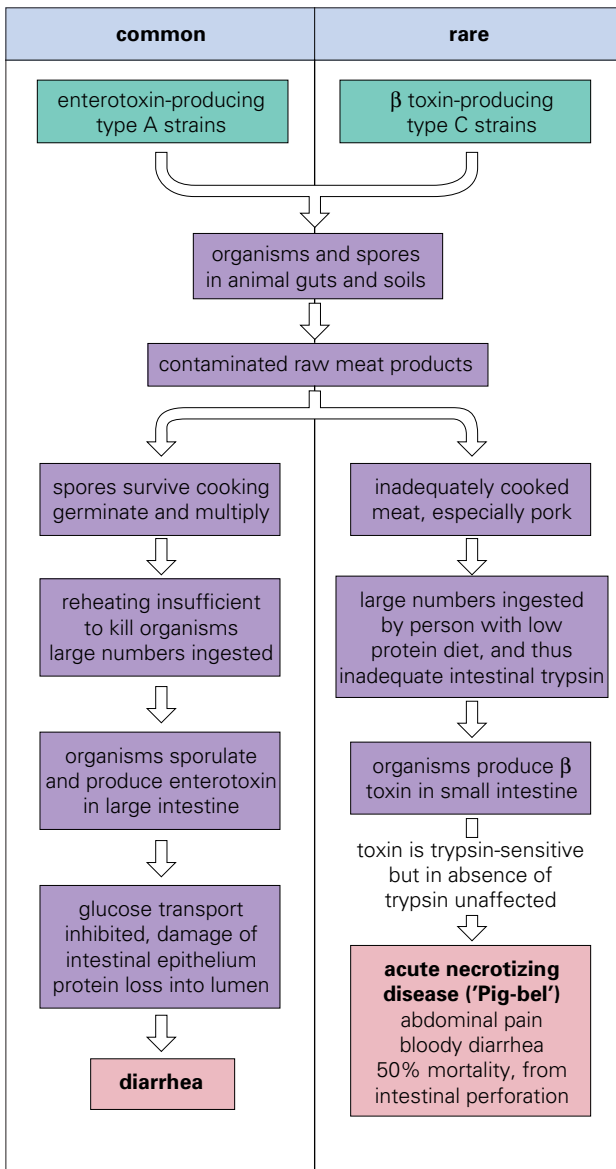


Fig. 20.21 *Clostridium perfringens* is linked with two forms of food-associated infection. The common, enterotoxin-mediated infection (left) is usually acquired by eating meat or poultry that has been cooked enough to kill vegetative cells, but not spores. As the food cools the spores germinate. If reheating before consumption is inadequate (as it often is in mass catering outlets), large numbers of organisms are ingested. The rare form associated with β toxin-producing strains (right) causes a severe necrotizing disease.

- Vomiting due to the ingestion of enterotoxin in food.

Two different toxins are involved, as illustrated in *Figure 20.22*. The clinical features of the infections are summarized in *Figure 20.12*. Laboratory confirmation of the diagnosis requires specific media as described in the Appendix. The emetic type of disease may be difficult to assign to *B. cereus* unless the incriminated food is cultured.

As with *Cl. perfringens*, prevention of *B. cereus* food-associated infection depends upon proper cooking and rapid consumption of food. Specific antibacterial treatment is not indicated.

Antibiotic-associated diarrhea – *Clostridium difficile*

Treatment with broad-spectrum antibiotics can be complicated by *Cl. difficile* diarrhea

All the infections described so far arise from the ingestion of organisms or their toxins. However, diarrhea can also arise

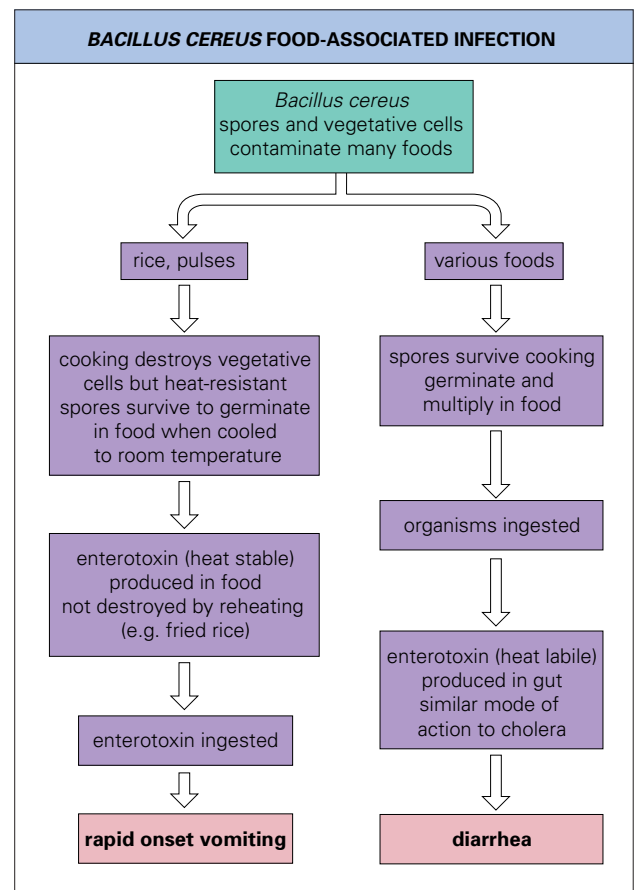


Fig. 20.22 *Bacillus cereus* can cause two different forms of food-associated infection. Both involve toxins.

from disruption of the normal gut flora. Even in the early days of antibiotic use it was recognized that these agents affected the normal flora of the body as well as attacked the pathogens. For example, orally-administered tetracycline disrupts the normal gut flora and patients sometimes become recolonized not with the usual facultative Gram-negative anaerobes, but with *Staphylococcus aureus*, causing enterocolitis, or with yeasts such as *Candida*. Soon after clindamycin was introduced for therapeutic use, it was found to be associated with a severe diarrhea in which the colonic mucosa became covered with a characteristic fibrinous pseudomembrane (pseudomembranous colitis; *Fig. 20.23*). However, clindamycin is not the cause of the condition; it merely inhibits the normal gut flora and allows *Cl. difficile* to multiply. This organism is commonly found in the gut of children and sometimes in adults, but can also be acquired from other patients in hospital by cross-infection. In common with other clostridia, *Cl. difficile* produces exotoxins, two of which have been characterized: one is a cytotoxin and the other an enterotoxin, and both appear to play a role in producing diarrhea.

Although initially associated with clindamycin, *Cl. difficile* diarrhea has since been shown to follow therapy with

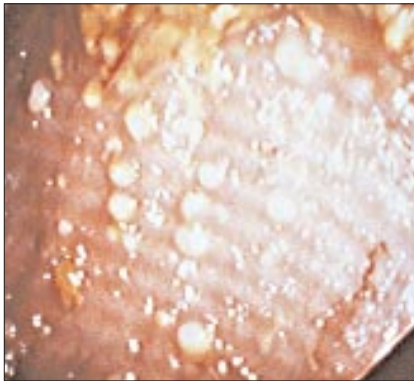


Fig. 20.23 Antibiotic-associated colitis due to *Clostridium difficile*. Sigmoidoscopic view showing multiple pseudomembranous lesions. (Courtesy of J Cunningham.)

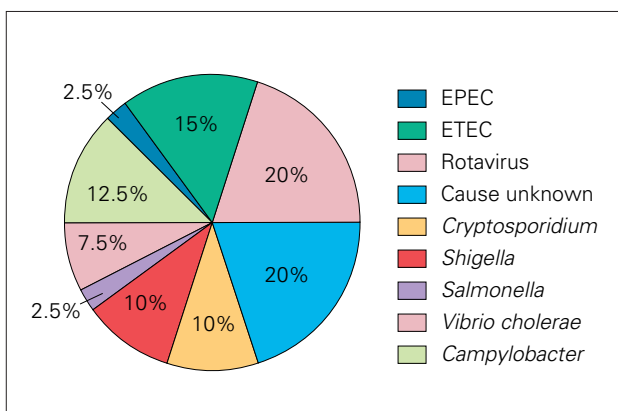


Fig. 20.24 Diarrheal disease is a major cause of illness and death in children in developing countries. This illustration shows the proportion of infections caused by different pathogens. Note that in as many as 20% of infections a cause is not identified, but many of these are likely to be viral. (Data from the WHO.) (ETEC, enterotoxigenic *Escherichia coli*; ETEC enterotoxigenic *E. coli*)

many other broad-spectrum antibiotics; hence the term antibiotic-associated diarrhea or colitis. The infection is often severe and requires treatment with the anti-anaerobic agent, metronidazole, or with oral vancomycin. However, the recent emergence of vancomycin-resistant enterococci, probably originating in the gut flora, has led to the recommendation that oral vancomycin is avoided wherever possible (see Chapter 30).

Viral diarrhea

Over three million infants die of gastroenteritis each year and viruses are the commonest cause

Non-bacterial gastroenteritis and diarrhea are usually caused by viruses. Infection is seen in all parts of the world, especially in infants and young children (*Fig. 20.24*). Its impact is staggering – in parts of Asia, Africa and Latin America more than three million infants die of gastroenteritis each year, and children may have a total of 60 days of diarrhea in each year. It has a major effect on nutritional status and growth. In the USA about 200 000 children less than five years of age are hospitalized each year due to infectious gastroenteritis.

Although viruses appear to be the commonest causes of gastroenteritis in infants and young children, viral gastroenteritis is not distinguishable clinically from other types of gastroenteritis. The viruses are specific to humans and infection follows the general rules for fecal–oral transmission. Oral transmission of non-bacterial gastroenteritis was first demonstrated experimentally in 1945, but it was not until 1972 that viral particles were identified in feces by electron microscopy. It has been difficult or impossible to cultivate most of these viruses in cell culture.

Rotaviruses

These are morphologically characteristic viruses (*Fig 20.25*), with a genome consisting of 11 separate segments of

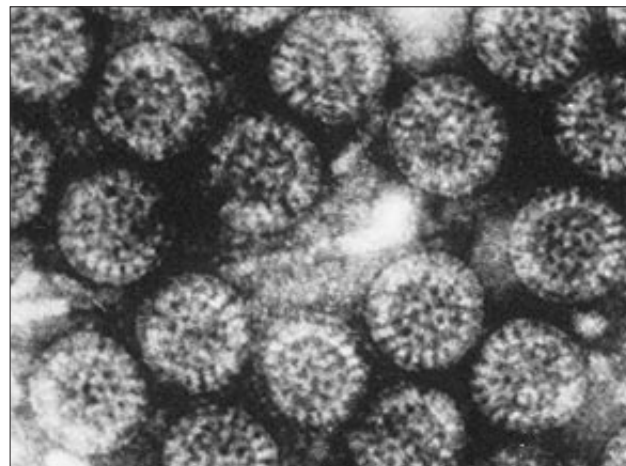


Fig. 20.25 Rotavirus. The virus particles (65 nm in diameter) have a well-defined outer margin and capsids radiating from an inner core to give the particle a wheel-like (hence 'rota') appearance. (Courtesy of JE Banatvala.)

double-stranded RNA. Different rotaviruses infect the young of many mammals, including children, kittens, puppies, calves, foals and piglets, but it is thought that viruses from one host species occasionally cross-infect another. There are at least two human serotypes.

Replicating rotavirus causes diarrhea by damaging transport mechanisms in the gut

The incubation period is 1–4 days. After virus replication in intestinal epithelial cells there is an acute onset of vomiting,

which is sometimes projectile, and diarrhea. The replicating virus damages transport mechanisms in the gut and loss of water, salt and glucose causes diarrhea (Fig. 20.26). Infected cells are destroyed, but there is no inflammation or loss of blood. Exceedingly large numbers of virus particles (10^{10} – 10^{11} /g) appear in the feces. For unknown reasons, respiratory symptoms (cough, coryza) are quite common. The disease is more severe in infants in developing countries.

Infection is commonest in children under two years of age, and most frequent in the cooler months of the year.

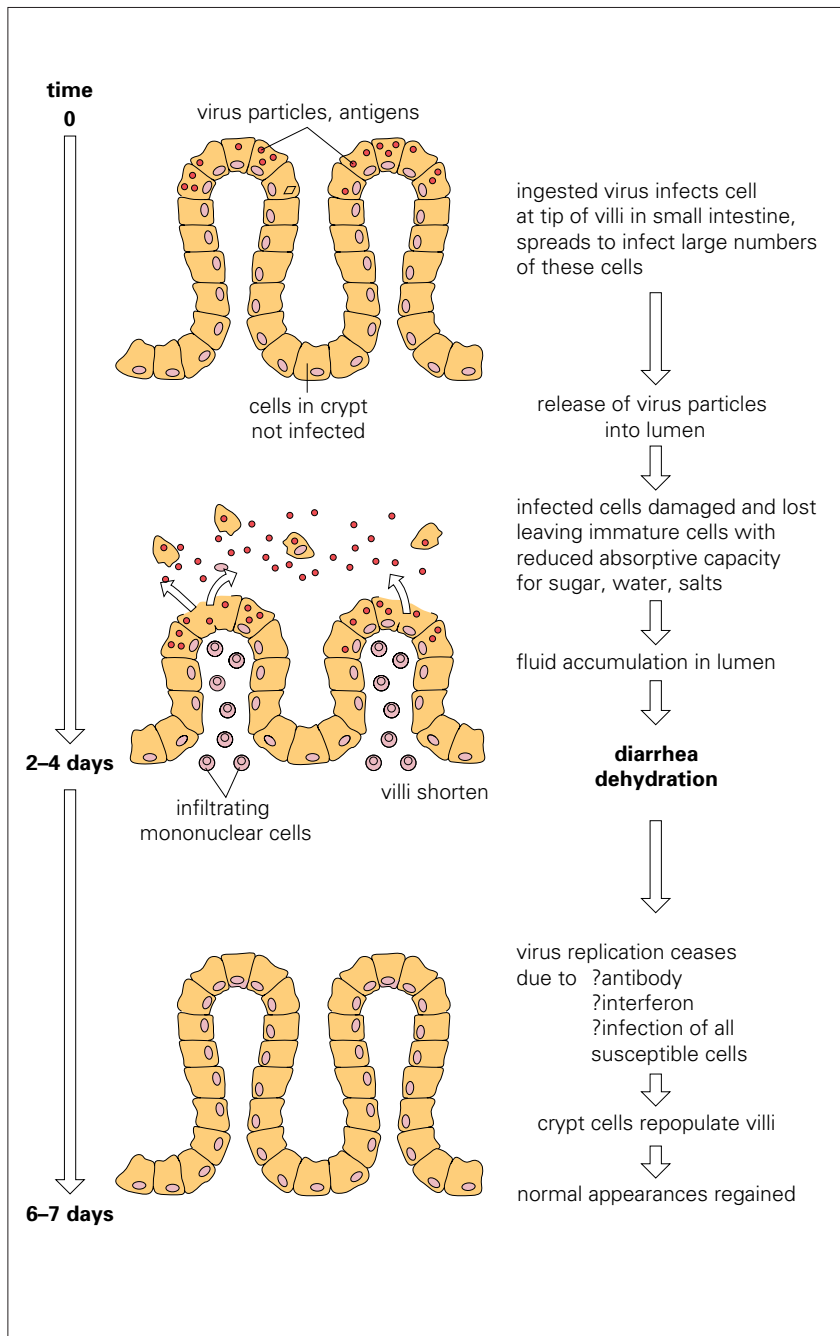


Fig. 20.26 The mechanism of rotavirus diarrhea. Other viruses may have different mechanisms.

IgA antibodies in colostrum give protection during the first six months of life. Epidemics are sometimes seen in nurseries. Older children are less susceptible, nearly all of them having developed antibodies, but occasional infections occur in adults.

Rotaviruses are well-adapted intestinal parasites. As few as 10 ingested particles can cause infection, and by generating a diarrhea laden with enormous quantities of infectious particles these organisms have ensured their continued transmission and survival.

Rotavirus particles can be seen in fecal samples by electron microscopy

Laboratory methods are generally not available in developing countries or necessary in developed countries, but during the acute stages the characteristic 65 nm particles can be seen in fecal samples by electron microscopy. They show cubic symmetry and an outer capsid coat arranged like the spokes of a wheel (Fig. 20.25). Viral antigen can be detected in feces by enzyme-linked immunosorbent assay (ELISA) or radioimmunoassay (RIA) methods (see Chapter 14).

Fluid and salt replacement can be life-saving in rotavirus diarrhea

Dehydration occurs readily in infants and fluid and salt replacement orally (or intravenously) can be life-saving. There are no antiviral agents available, but a variety of live attenuated oral vaccines are undergoing trials.

Other viruses

Other viruses causing diarrhea include caliciviruses, astroviruses, adenoviruses, parvoviruses and coronaviruses

Caliciviruses are 27 nm single-stranded RNA viruses that may cause ‘winter vomiting disease’. They include the small round-structured viruses. One representative is the Norwalk virus, which has not yet been cultivated *in vitro*, but causes gastroenteritis when fed to adult volunteers. One of the first identified outbreaks was in a school in Norwalk, Ohio in 1969. Infection is common in older children and adults. In 25–50% of cases there may be chills, headache, myalgia or fever as well as nausea, vomiting and diarrhea, but recovery occurs within about 24 hours and laboratory diagnosis is unnecessary. Viruses in this group are often implicated in diarrhea, occurring after eating sewage-contaminated shellfish such as cockles or mussels.

Astroviruses are 28 nm single-stranded RNA viruses of which five serotypes are known. Most infections occur in childhood and are mild. Adenoviruses (especially types 40 and 41) are second to rotaviruses as a cause of acute diarrhea in young children. Most cannot be grown in cell culture. Parvoviruses and coronaviruses have an uncertain role.

Although outbreaks of gastroenteritis often have a viral etiology it may be difficult to be sure about the exact role of a given virus when it is identified in feces.

Food poisoning

In this chapter the term ‘food poisoning’ is restricted to the diseases caused by toxins elaborated by contaminating bacte-

ria in food before it is consumed (see above). The emetic toxin of *B. cereus* fits this definition, as do the diseases associated with the consumption of *Staph. aureus* enterotoxin and *Cl. botulinum* toxin.

Staphylococcus aureus

Five different enterotoxins are produced by different strains of Staph. aureus

Five serologically distinct enterotoxins (A–E) are produced by strains of *Staph. aureus* (Fig. 20.27). All are heat stable and resistant to destruction by enzymes in the stomach and small intestine. Their mechanism of action is not understood, but they have an effect on the central nervous system that results in severe vomiting within 3–6 hours of consumption. Diarrhea is not a feature and recovery within 24 hours is usual.

Up to 50% of *Staph. aureus* strains produce enterotoxin, and food (especially processed meats) is contaminated by human carriers. The bacteria grow at room temperature and release toxin. Subsequent heating may kill the organisms, but the toxin is stable. Often there are no viable organisms detectable in the food consumed, but enterotoxin can be detected by a latex agglutination test.

Botulism

Exotoxins produced by Cl. botulinum cause botulism

Botulism is a rare but serious disease caused by the exotoxin of *Cl. botulinum*. The organism is widespread in the environment and spores can be isolated readily from soil samples and from various animals including fish. Eight serologically distinct toxins have been identified, but only three – A, B and E – are associated with human disease (Fig. 20.28). The toxins are ingested in food (often canned or reheated) or produced in the gut after ingestion of the organism; they are absorbed from the gut into the bloodstream and then reach their site of action, the peripheral

STAPHYLOCOCCAL ENTEROTOXINS	
enterotoxin	
A	most commonly associated with food poisoning
B	associated with staphylococcal enterocolitis (rare)
C	rare
D	second most common, alone or in combination with A
E	rare
	} associated with contaminated milk products

Fig. 20.27 *Staphylococcus aureus* produces five immunologically distinct enterotoxins. Strains may produce one or more of the toxins simultaneously. Enterotoxin A is by far the most common in food-associated disease.

TOXINS OF <i>CLOSTRIDIUM BOTULINUM</i>		
antigenically distinct polypeptides		
types: A B E	} human disease	
types: C D		} animal botulism
relative heat labile, destroyed at 80°C for 30 minutes		
not destroyed by digestive enzymes		

Fig. 20.28 Eight different *Clostridium botulinum* toxins have been identified, but of these only three are associated with human disease and two others with botulism in animals. These protein exotoxins are the most potent biologic toxins known to man. They are antigenic and can be inactivated and used to produce antitoxin in animals.



Fig. 20.29 *Helicobacter pylori* gastritis. Silver stain showing numerous spiral-shaped organisms adhering to the mucosal surface. (Courtesy of AM Geddes.)

nerve synapses. The action of the toxin is to block neurotransmission (see Chapter 12).

Infant botulism is the most common form of botulism

There are three forms of botulism:

- Foodborne botulism.
- Infant botulism.
- Wound botulism.

In foodborne botulism, toxin is elaborated by organisms in food, which is then ingested. In infant and wound botulism, the organisms are respectively ingested or implanted in a wound, and multiply and elaborate toxin *in vivo*. Infant botulism has been associated with feeding babies honey contaminated with *Cl. botulinum* spores.

The clinical disease is the same in all three forms and is characterized by flaccid paralysis leading to progressive muscle weakness and respiratory arrest. Intensive supportive treatment is urgently required and complete recovery may take many months. Improvements in supportive care have reduced the mortality from around 70% to approximately 10%, but the disease, although rare, remains life-threatening.

Laboratory diagnosis of botulism involves injecting fecal and food samples into mice

Laboratory diagnosis depends largely upon demonstrating the presence of toxin by injecting samples of feces and food (if available) into mice that have been protected with botulinum antitoxin or left unprotected. There are no *in vitro* tests routinely available at present. Culture of feces or wound exudate for *Cl. botulinum* should also be performed.

Polyvalent antitoxin is recommended as an adjunct to intensive supportive therapy for botulism

Antibacterial agents are not helpful. It is not practicable to prevent food becoming contaminated with botulinum spores so prevention of disease depends upon preventing the germination of spores in food by:

- Maintaining food at an acid pH.
- Storing food at less than 4°C.
- Destroying toxin in food by heating for 30 minutes at 80°C.

***Helicobacter pylori* and Gastric Ulcer Disease**

***Helicobacter pylori* is associated with most duodenal and gastric ulcers**

It is now well established that the Gram-negative spiral bacterium *H. pylori* is associated with over 90% of duodenal ulcers and 70–80% of gastric ulcers (Fig. 20.29). The role of *H. pylori* in functional or non-ulcer dyspepsia, which most commonly presents with persistent or recurrent pain in the upper abdomen in the absence of structural evidence of disease, is less clear. Diagnosis is usually made on the basis of histologic examination of biopsy specimens, although non-invasive tests such as the urea breath test (*H. pylori* produces large amounts of urease) are being increasingly used. *H. pylori* can be cultured in the laboratory, but it is not an easy organism to grow.

The mechanism of pathogenicity has still to be identified, but cytotoxin production has been described. The large amounts of urease produced by the organism may assist its survival in the acid environment of the gastric mucosa.

Eradication of *H. pylori* leads to the remission and healing of ulcers without the need for acid suppression, but successful treatment requires combination therapy. The most promising regimens to date employ the combination of a proton pump inhibitor and two antibiotics (e.g. omeprazole with amoxicillin and metronidazole or clarithromycin (a new macrolide, see Chapter 30).

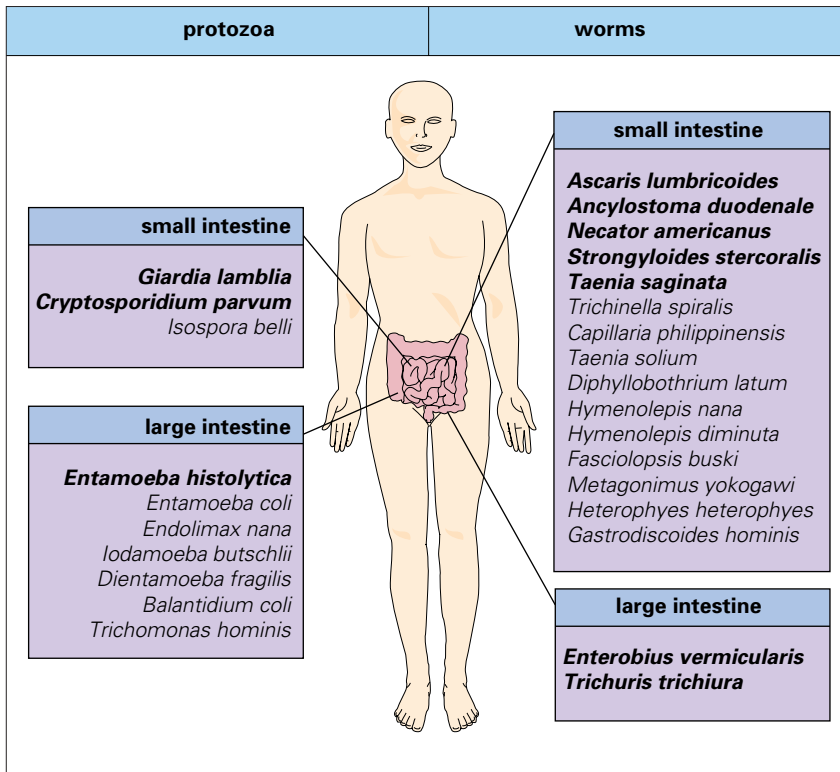


Fig. 20.30 Gastrointestinal parasites of man. The majority of these infections are found in developing countries, but all species also occur in the developed world and some have recently come to prominence because of their association with AIDS. The most important parasite species are highlighted in bold type.

Parasites and the Gastrointestinal Tract

Many species of protozoan and worm parasites live in the gastrointestinal tract, but only a few are a frequent cause of serious pathology (Fig. 20.30). These will form the focus of this section.

Transmission of intestinal parasites is maintained by the release of life cycle stages in feces

The different life cycle stages include cysts, eggs and larvae. In most cases new infections depend either directly or indirectly upon contact with fecally-derived material, infection rates therefore reflecting standards of hygiene and levels of sanitation. In general, the stages of protozoan parasites passed in feces are either already infective or become infective within a short time. These parasites are therefore usually acquired by swallowing infective stages in fecally-contaminated food or water. Worm parasites, with two major exceptions (pinworms and tapeworms), produce eggs or larvae that require a period of development outside the host before they become infective. Transmission routes are more complex here:

- Some species are acquired through food or water contaminated with infective eggs or larvae, or are picked up directly via contaminated fingers.
- Some have larvae that can actively penetrate through the skin, migrating eventually to the intestine.
- Others are acquired by eating animals or animal products containing infective stages.

The symptoms of intestinal infection range from very mild, through acute or chronic diarrheal conditions associated with parasite-related inflammation, to life-threatening diseases caused by spread of the parasites into other organs of the body. Most infections fall into the first of these categories; indeed, in many parts of the world, intestinal parasitism is accepted as a normal condition of life.

Protozoan infections

Three species are of particular importance:

- *Entamoeba histolytica*.
- *Giardia lamblia*.
- *Cryptosporidium parvum*.

All three can give rise to diarrheal illnesses, but the organisms have distinctive features that allow a differential diagnosis to be made quite easily (Fig. 20.31).

Entamoeba histolytica

***Entamoeba histolytica* infection is particularly common in subtropical and tropical countries**

Infections with *Entamoeba histolytica* occur worldwide, but are most often found in subtropical and tropical countries where the prevalence may exceed 50%. The trophozoite stages of the amebae live in the large intestine on the mucosal surface, frequently as harmless commensals feeding on bacteria. Reproduction of these stages is by simple binary fission, and there is periodic formation of resistant encysted forms, which pass out of the body. These cysts can survive in the external environment and act as the infective stages; asymptomatic individuals are therefore carriers capable of infecting

others. Infection occurs when food or drink is contaminated either by infected food handlers or as a result of inadequate sanitation. Transmission can also take place as a result of anal sexual activity. The cysts pass intact through the stomach when swallowed and excyst in the small intestine, each giving rise to eight progeny. Under certain conditions, still undefined, but including variables of both host and parasite origin, *Entamoeba* can become pathogenic, the amebae invading the mucosa and feeding on host materials including red blood cells, giving rise to amebic colitis.

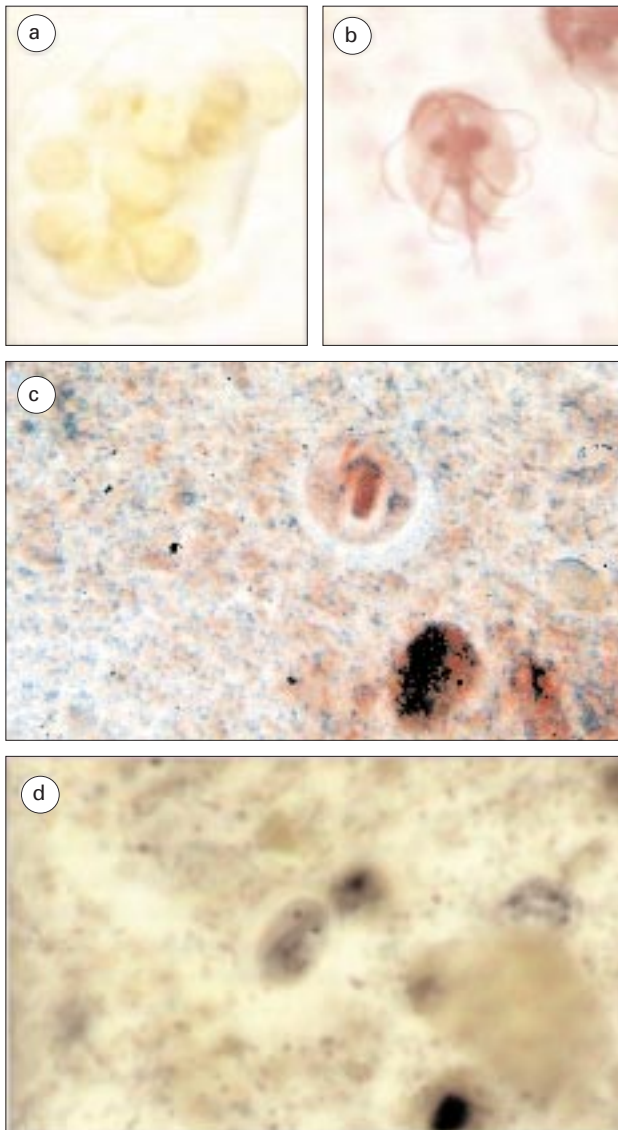


Fig. 20.31 Protozoan infections of the gastrointestinal tract. (a) *Entamoeba histolytica*. Trophozoite found in the acute stage of the disease, which often contains ingested red blood cells. (b) *Giardia lamblia* trophozoite associated with acute infection in man. (Courtesy of DK Banerjee.) (c) Cyst of *E. histolytica*, with only one of the four nuclei visible. The broad chromatid bar is a semicrystalline aggregation of ribosomes. Hematoxylin and eosin stain. (d) Oval cyst of *G. lamblia* showing two of the four nuclei. Iron hematoxylin stain. (Courtesy of R Muller and JR Baker.)

The clinical manifestations of *E. histolytica* infection vary from asymptomatic to severe dysentery

Infections with commensal forms of the ameba are asymptomatic. Invasion of the mucosa may produce small localized superficial ulcers or involve the entire colonic mucosa with the formation of deep confluent ulcers (Fig. 20.32). The former causes a mild diarrhea, whereas more severe invasion leads to ‘amebic dysentery’, which is characterized by mucus, pus and blood in the stools. Dysenteries of amebic and bacillary origin can be distinguished by a number of features (Fig. 20.33).

Complications include perforation of the intestine, leading to peritonitis, and extraintestinal invasion. Trophozoites can spread via the blood to the liver, with the formation of an abscess, and may secondarily extend to the lung and other organs. Rarely, abscesses spread directly and involve the overlying skin.

***E. histolytica* infection can be diagnosed from the presence of characteristic four-nucleate cysts in the stool**

These cysts may be infrequent in light infections and repeated stool examination is necessary. Care must be taken

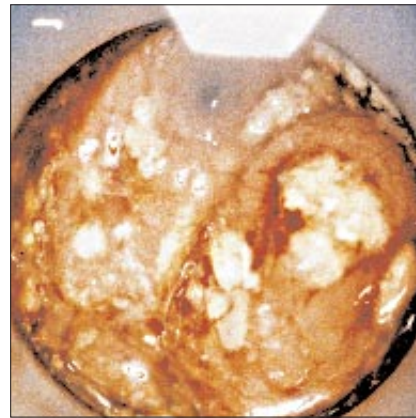


Fig. 20.32 Amebic colitis. Sigmoidoscopic view showing deep ulcers and overlying purulent exudate. (Courtesy of RH Gilman.)

FEATURES OF BACILLARY AND AMEBIC DYSENTERY		
	bacillary	amebic
organism	shigella	entameba
polymorphs and macrophages in stool	many	few
eosinophils and Charcot-Leydon crystals in stool	few or absent	often present
organisms in stool	many	few
blood and mucus in stool	yes	yes

Fig. 20.33 Features of bacillary and amebic dysentery.

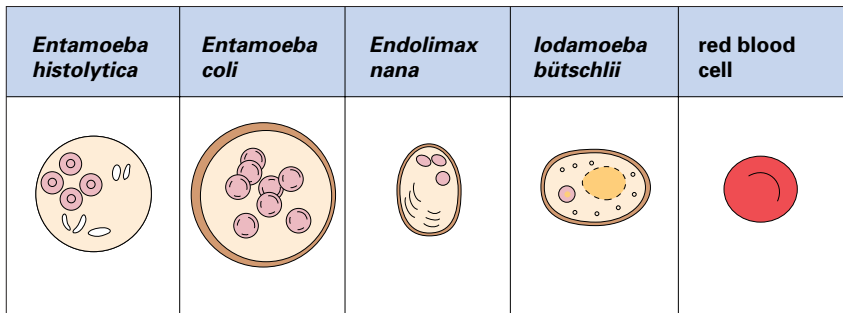


Fig. 20.34 Characteristics of cysts (size and number of nuclei) are used to differentiate pathogenic from non-pathogenic protozoa. A red blood cell is shown for comparison.

to differentiate *E. histolytica* from other non-pathogenic species that might be present (Fig. 20.34). Trophozoites can be found in cases of dysentery (when the stools are loose and wet), but they are fragile and deteriorate rapidly; specimens should therefore be preserved before examination. Several immunologic tests are available, but only indicate whether patients have been exposed to infection at some time in their history, though they can be useful in confirming a preliminary diagnosis.

Acute *E. histolytica* infection can be treated with metronidazole

Recovery from infection is usual and there is some immunity to reinfection. Treatment may fail to clear the infection completely and the passage of infective cysts can continue. Metronidazole is useful against the extraintestinal sites of infection, but if these become secondarily infected with bacteria, additional antibiotics and drainage are necessary. Prevention of amebiasis in the community requires the same approaches to hygiene and sanitation as those adopted for bacterial infections of the intestine.

Giardia lamblia

Giardia was the first intestinal microorganism to be observed under a microscope. It was discovered by Anton van Leeuwenhoek in 1681, using the microscope he had invented to examine specimens of his own stool. At the present time it is the most commonly diagnosed intestinal parasite in the USA.

Like *Entamoeba*, *Giardia* has only two life cycle stages

The two life cycle stages are the flagellate (four pairs of flagella) binucleate trophozoite and the resistant four-nucleate cyst. The trophozoites live in the upper portion of the small intestine, adhering closely to the brush border of the epithelial cells by specialized attachment regions (Fig. 20.35). They divide by binary fission and can occur in such numbers that they cover large areas of the mucosal surface. Cyst formation occurs at regular intervals, each cyst being formed as one trophozoite rounds up and produces a resistant wall. Cysts pass out in the stools and can survive for several weeks under optimum conditions. Infection occurs when the cysts are swallowed, usually as a result of drinking contaminated water. Epidemics of giardiasis have occurred when public drinking supplies have become contaminated, but smaller outbreaks

have been traced to drinking from rivers and streams that have been contaminated by wild animals. The genus *Giardia* is widely distributed in mammals and there is suggestive evidence for cross-infection between certain animal hosts (e.g. beaver) and humans. Much of this is circumstantial, but case reports provide more direct evidence. Recent data suggest that *Giardia* may also be transmitted sexually.

Mild *Giardia* infections are asymptomatic, more severe infections cause diarrhea

The diarrhea may be:

- Self-limiting, with 7–10 days being the usual course.
- Chronic, and develop into a serious condition, particularly in patients with deficient or compromised immunologic defenses.

It is thought to arise from inflammatory responses triggered by the damaged epithelial cells and from interference with normal absorptive processes. Characteristically the stools are loose, foul-smelling and often fatty.

Diagnosis of *Giardia* infection is based on identifying cysts or trophozoites in the stool

Repeated examination is necessary in light infections when concentration techniques improve the chances of finding cysts. Duodenal intubation or the use of recoverable swallowed capsules and threads may aid in obtaining trophozoites directly from the intestine.

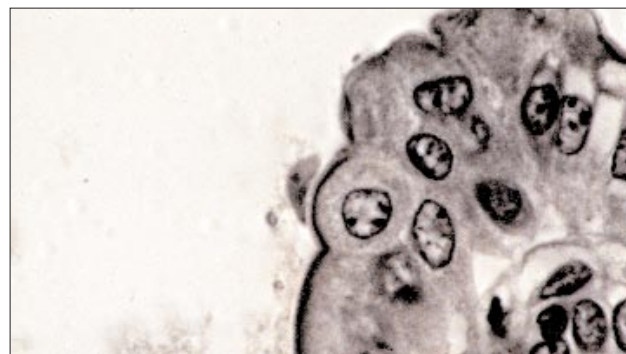


Fig. 20.35 Trophozoite of *Giardia lamblia* attached to the mucosal surface of the small intestine. Iron hematoxylin stain. (Courtesy of R Muller and JR Baker.)

***Giardia* infection can be treated with a variety of drugs**

These include mepacrine hydrochloride, metronidazole and tinidazole, but none is completely successful. Community measures for prevention include the usual concerns with hygiene and sanitation, and improved treatment of drinking water supplies (largely filtration and chlorination) where these are suspected as a source. Care in drinking from potentially-contaminated natural waters is also indicated.

Cryptosporidium parvum

***Cryptosporidium parvum* is widely distributed in many animals**

The implication of *Cryptosporidium parvum* as a cause of diarrhea in humans is comparatively recent (within the last 10–15 years). The parasite is widely distributed in many animals, but is very small and easily overlooked. It has a complex life cycle, going through both asexual and sexual phases of development in the same host. Transmission is by ingestion of about 100 of the resistant oocyst stage (4–5 µm diameter) in fecally-contaminated material (Fig. 20.36). In the small intestine the cyst releases infective sporozoites, which invade the epithelial cells, remaining closely associated with the apical plasma membrane. Here they form schizonts, which divide to release merozoites and these then reinvade further epithelial cells. Eventually a sexual phase occurs and oocysts are released. Transmission probably occurs most often via drinking water contaminated by oocysts, either from other humans or from animals. In 1993, *C. parvum* caused a massive outbreak of watery diarrhea affecting 403 000 people in Milwaukee, USA. It was transmitted through the public water supply and probably originated from cattle.

***C. parvum* diarrhea ranges from moderate to severe**

Symptoms of infection with *C. parvum* range from a moderate diarrhea to a more severe profuse diarrhea that is self-limiting in immunocompetent individuals (lasting up to 20 days), but can become chronic in immunocompromised patients. Cryptosporidiosis is a common infection in people with AIDS. In these individuals diarrhea is prolonged, may become irreversible, and can be life-threatening.

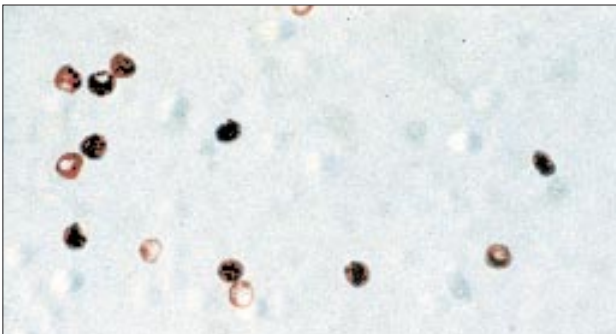


Fig. 20.36 *Cryptosporidium* oocysts in fecal specimen. (Courtesy of S Tzipori.)

Routine fecal examinations are inadequate for diagnosing *C. parvum* diarrhea

Concentration techniques and special staining (e.g. modified acid-fast stain) are necessary to recover and identify the oocysts.

Only immunocompromised patients need treatment for *C. parvum* diarrhea

The macrolide spiramycin has been used for immunocompromised patients with limited success. Public health measures are similar to those outlined for controlling giardiasis, although *Cryptosporidium* is more resistant to chlorination.

Worm infections

The most important intestinal worms clinically are the nematodes known as ‘soil-transmitted helminths’

Soil-transmitted helminths fall into two distinct groups:

- *Ascaris lumbricoides* (large roundworm) and *Trichuris trichiura* (whipworm), in which infection occurs by swallowing the infective eggs.
- *Ancylostoma duodenale* and *Necator americanus* (hookworms) and *Strongyloides stercoralis*, which infect by active skin penetration by infective larvae, which then undertake a systemic migration through the lungs to the intestine.

With the exception of *Trichuris* (large intestine), all inhabit the small bowel.

The pinworm or threadworm *Enterobius vermicularis* is perhaps the commonest intestinal nematode in developed countries and is the least pathogenic. The females of this species, which live in the large bowel, release infective eggs onto the perianal skin. This causes itching and transmission usually occurs directly from contaminated fingers, but the eggs are also light enough to be carried in dust.

The soil-transmitted helminths are commonest in the warmer developing countries. About 25% of the world’s population carry these worms, children being the most heavily infected section of the population. Transmission is favored where there is inadequate disposal of feces, contamination of water supplies, use of feces (night-soil) as fertilizer, or low standards of hygiene (see below). Vast numbers of eggs are formed by each female (tens of thousands by *Trichuris* and *Ancylostoma* and hundreds of thousands by *Ascaris*).

Life cycle and transmission

Female *Ascaris* and *Trichuris* lay thick-shelled eggs in the intestine, which are expelled with feces and hatch after being swallowed by another host

The thick-shelled eggs of *Ascaris* and *Trichuris* are shown in Figure 20.37. The eggs require incubation for several days at optimum conditions (warm temperature, high humidity) for the infective larvae to develop. Once this occurs, the eggs remain infective for many weeks or months, depending upon the local microclimate. After being swallowed the eggs hatch in the intestine, releasing the larvae. Those of *Ascaris* penetrate the gut wall and are carried in the blood through the liver to the lungs, climbing up the bronchi and trachea before being swallowed and once again reaching the intestine. The adult worms live freely in the gut lumen, feeding on intestinal

contents. In contrast *Trichuris* larvae remain within the large bowel, penetrating into the epithelial cell layer, where they remain as they mature.

Adult female hookworms lay thin-shelled eggs that hatch in the feces shortly after leaving the host

A hookworm egg is shown in *Figure 20.37*. The larvae of these hookworms (*A. duodenale* and *N. americanus*) feed on bacteria until infective, and then migrate away from the fecal mass. Infection takes place when larvae come into contact with unprotected skin (or additionally, in the case of *Ancylostoma*, are swallowed). They penetrate the skin, migrate via the blood to the lungs, climb the trachea and are swallowed. Adult worms attach by their enlarged mouths to the intestinal mucosa, ingest a plug of tissue, rupture capillaries and suck blood.

The adult female *Strongyloides* lays eggs that hatch in the intestine

The life cycle of *Strongyloides* is similar to that of hookworms, but shows some important differences. The adult worm exists as a parthenogenetic female that lays eggs into the mucosa. These eggs hatch in the intestine and the released larvae usually pass out in the feces (*Fig. 20.37*). Development outside the host can follow the hookworm pattern, with the direct production of skin-penetrating larvae or may be diverted into the production of a complete free-living generation, which then produces infective larvae. Under certain conditions, and particularly when the host is immunocompromised, *Strongyloides* larvae can reinvade before they are voided in the

feces. This process of autoinfection can give rise to the severe clinical condition known as ‘disseminated strongyloidiasis’. All soil-transmitted helminths are relatively long-lived (several months to years), but authenticated cases show that strongyloides infections can persist for more than 30 years, presumably through continuous internal autoinfection.

Clinical features

In most individuals, worm infections produce chronic mild intestinal discomfort rather than severe diarrhea or other conditions. Each infection has a number of characteristic pathologic conditions linked with it.

Large numbers of adult *Ascaris* worms can cause intestinal obstruction

The migration of *Ascaris* larvae through the lungs can cause severe respiratory distress (pneumonitis) and this stage is often associated with pronounced eosinophilia. Intestinal stages of infection can cause abdominal pain, nausea and digestive disturbances. In children with a suboptimal nutritional intake these disturbances can contribute to clinical malnutrition. Large numbers of adult worms can cause a physical blockage in the intestine and this may also occur as worms die following chemotherapy. Intestinal worms tend to migrate out of the intestine, often up the bile duct, causing cholangitis. Perforation of the intestinal wall can also occur. Worms have occasionally been reported in unusual locations, including the orbit of the eye and the (male) urethra. *Ascaris* is highly allergenic and infections often give rise to symptoms of hypersensitivity, which may persist for many years after the infection has been cleared.

Moderate to severe *Trichuris* infection can cause a chronic diarrhea

As with all intestinal worms, children are the members of the community most heavily infected with *Trichuris*. Although usually regarded as of little clinical significance, recent research has shown that moderate to heavy infections in children can cause a chronic diarrhea (*Fig. 20.38*), reflected in impaired nutrition and retarded growth. Occasionally heavy infections lead to prolapse of the rectum.

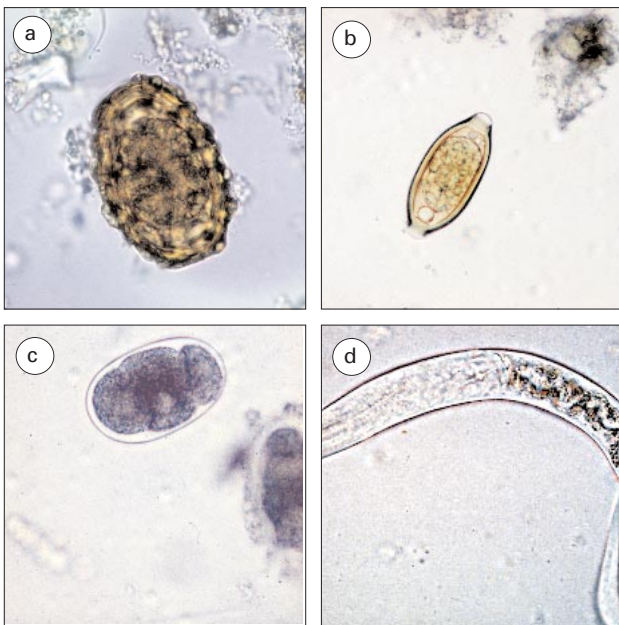


Fig. 20.37 Eggs and larvae of intestinal nematodes passed in feces. (a) Egg of *Ascaris* (fertile). (b) Egg of *Trichuris*. (c) Egg of hookworm. The ovum continues to divide in the fecal sample and may be at the 16- or 32-cell stage by the time the sample is examined. (d) Larva of *Strongyloides stercoralis*. (Courtesy of JH Cross.)

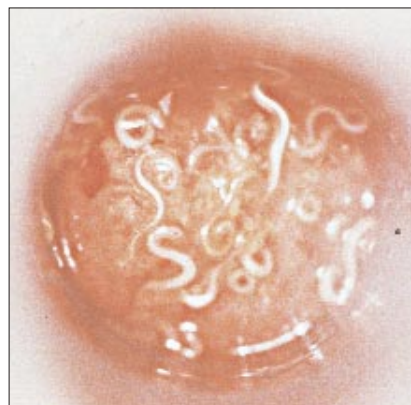


Fig. 20.38 Trichuriasis in a healthy, infected, child. Proctoscopic view showing numerous adult *Trichuris trichiura* attached to the intestinal mucosa. (Courtesy of RH Gilman.)

Hookworm disease can result in an iron-deficiency anemia

Invasion of hookworm larvae through the skin and lungs can cause a dermatitis and pneumonitis, respectively. The blood-feeding activities of the intestinal worms can lead to an iron-deficiency anemia if the diet is inadequate. Heavy infections cause a marked debility and growth retardation.

Strongyloidiasis can be fatal in immunosuppressed people

Heavy intestinal infection with *Strongyloidiasis* causes a persistent and profuse diarrhea with dehydration and electrolyte imbalance. Profound mucosal changes can also lead to a malabsorption syndrome, which is sometimes confused with tropical sprue. People with diseases that suppress immune function such as AIDS and cancer or who are being treated with immunosuppressant drugs are susceptible to the development of disseminated strongyloidiasis. Invasion of the body by many thousands of autoinfective larvae can be fatal.

The commonest sign of pinworm (threadworm) infection is anal pruritus. Occasionally this is accompanied by mild diarrhea. Migrating worms sometimes invade the appendix and have been linked with appendicitis. Invasion of the vagina has been reported in female children.

Laboratory diagnosis

All five of the soil-transmitted species can be diagnosed by finding eggs or larvae in the fresh stool and direct smears or concentration techniques can be used. Immunodiagnosis of intestinal parasites is still at an early stage. Infections with *Ascaris*, hookworms and *Strongyloides* are often accompanied by a marked blood eosinophilia. Although this is not diagnostic, it is a strong indicator of worm infection.

The eggs of *Ascaris*, *Trichuris* and hookworms are characteristic

These eggs are shown in *Figure 20.37* and are easily recognizable. Identification of the species of hookworm requires culture of the stool to allow the eggs to hatch and the larvae to mature into the infective third stage. The presence of adult *Ascaris* can sometimes be confirmed directly by radiography (*Fig. 20.39*).

The presence of larvae in fresh stools is diagnostic of *Strongyloides* infection.

Pinworm infection is diagnosed by finding eggs on perianal skin

Although adult pinworms sometimes appear in the stools, the eggs are seldom seen because they are laid directly onto the perianal skin (*Fig. 20.40*). They can be found by wiping this area with a piece of clear adhesive tape (the ‘Scotch tape’ test) and examining the tape under the microscope.

Treatment and prevention

A variety of anthelmintic drugs is available for treating intestinal nematodes. Piperazine has been used with great success against *Ascaris*, hookworms and pinworm, though many more recent drugs (albendazole, mebendazole, levamisole, pyrantel) can also be used and are also effective against

trichuriasis and strongyloidiasis (especially albendazole and levamisole). At the community level, prevention can be achieved through improved hygiene and sanitation, making sure that fecal material is disposed of properly.

Other intestinal worms

Many other worm species can infect the intestine, but most are uncommon in developed countries

Of the human tapeworms:

- The beef tapeworm *Taenia saginata*, transmitted through infected beef, is the most widely distributed. However, infection is usually asymptomatic, apart from the nausea felt on passing the large segments! Diagnosis involves finding these segments or the characteristic eggs in the stool (*Fig. 20.41*).
- *Diphyllobothrium latum*, the broadfish tapeworm, is widely distributed geographically, but infection is restricted to individuals eating raw or undercooked fish carrying the infective larvae. The eggs of this species have a terminal ‘lid’ and are the diagnostic stage in the stool (*Fig. 20.42*).
- *Hymenolepis nana*, the dwarf tapeworm, occurs primarily in children, infection occurring directly by swallowing eggs (*Fig. 20.42*). This worm has the ability to undergo autoinfection within the host’s intestine, so that a large number of worms can build up rapidly, leading to diarrhea and some abdominal discomfort.

All these tapeworms can be removed by praziquantel or niclosamide.

Intestinal symptoms (predominantly diarrhea and abdominal pain) are also associated with infections by the nematode *Trichinella spiralis*, which is better known clinically for the pathology caused by the blood-borne muscle phase (see Chapters 23 and 26). Infection with the two species of schistosome associated with mesenteric blood vessels (*Schistosoma*



Fig. 20.39 Filling defect in the small intestine due to the presence of *Ascaris* seen on a radiograph after a barium meal. (Courtesy of W Peters.)

japonicum and *S. mansoni*) can also cause symptoms of intestinal disease. As the eggs pass through the intestinal wall they cause marked inflammatory responses, granulomatous lesions form, and diarrhea may occur in the early acute phase. Heavy chronic *S. mansoni* infection is associated with inflammatory polyps in the colon, while severe involvement of the small bowel is more common with *S. japonicum*.

Systemic Infection Initiated in the Gastrointestinal Tract

We opened this chapter by noting that infections acquired by the ingestion of pathogens could remain localized in the gastrointestinal tract or could disseminate to other organs and body systems. Important examples of disseminated infection are the enteric fevers and viral hepatitis type A and E. Listeriosis also appears to be acquired via the gastrointestinal tract. For the sake of clarity and convenience, other types of viral hepatitis will also be discussed in this chapter.



Fig. 20.40 Egg of *Enterobius* on perianal skin. (Courtesy of JH Cross.)

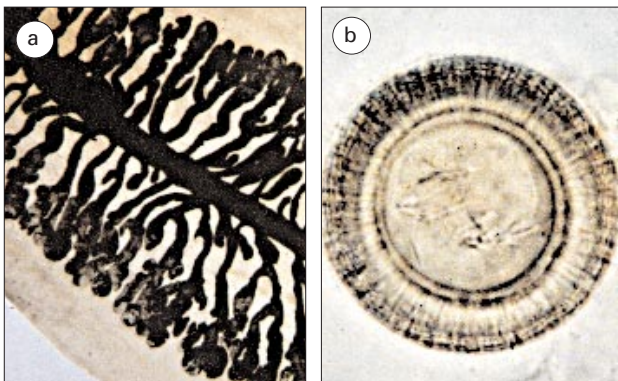


Fig. 20.41 *Taenia saginata*. (a) Gravid proglottids stained with India ink to show numerous side branches. (b) Egg containing six-hooked (hexacanth) larva. (Courtesy of R Muller and JR Baker.)

Enteric fevers: typhoid and paratyphoid

The term ‘enteric fever’ was introduced in the last century in an attempt to clarify the distinction between typhus (see Chapter 30) and typhoid. For many years these two diseases had been confused, as the common root of their names suggests (typhus, a fever with delirium; typhoid, resembling typhus), but even before the causative agents were isolated (typhoid caused by *S. typhi* and typhus caused by *Rickettsia* spp.), it was pointed out that it was ‘just as impossible to confuse the intestinal lesions of typhoid with the pathologic findings of typhus as it was to confuse the eruptions of measles with the pustules of smallpox’. In fact, enteric fevers can be caused by *S. paratyphi* as well as *S. typhi*, but the name ‘typhoid’ has stuck.

S. typhi and *S. paratyphi* types A, B and C cause enteric fevers

These species of *Salmonella* are restricted to humans and do not have a reservoir in animals. Therefore, spread of the infection is from person to person, usually through contaminated food or water. After infection, people can carry the organism for months or years, providing a continuing source from which others may become infected. Typhoid Mary, a cook in New York City in the early 1900s, is one such example. She was a long-term carrier who succeeded in initiating at least 10 outbreaks of the disease.

The salmonellae multiply within, and are transported around, the body in macrophages

After ingestion, the salmonellae that survive the antibacterial defenses of the stomach and small intestine penetrate the gut mucosa through the Peyer’s patches, probably in the jejunum or distal ileum (Fig. 20.43). Once through the mucosal barrier, the bacteria reach the intestinal lymph nodes, where they survive and multiply within macrophages (see Fig. 10.5). They are transported in the macrophages to the mesenteric lymph nodes and thence to the thoracic duct and are eventually discharged into the bloodstream. Circulating in the blood, the organisms can seed many organs, most importantly in areas where cells of the

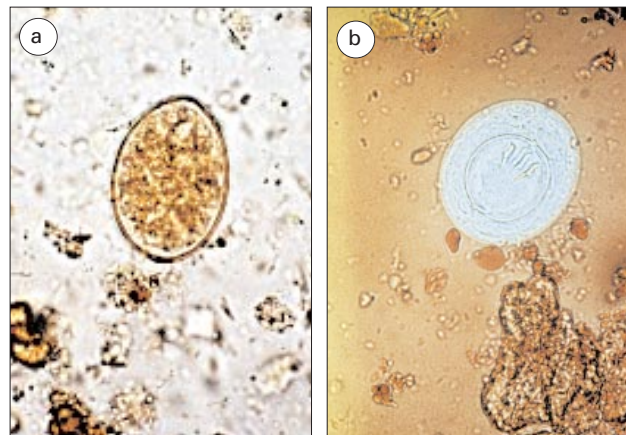


Fig. 20.42 Eggs of (a) *Diphyllobothrium latum* and (b) *Hymenolepis nana*. (Courtesy of R Muller and JR Baker.)

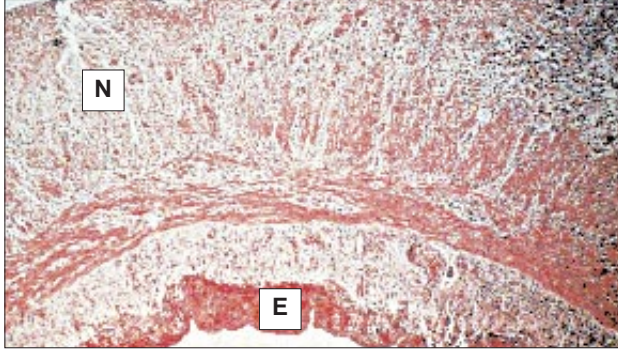


Fig. 20.43 Typhoid. Section of ileum showing a typhoid ulcer with a transmurular inflammatory reaction, focal areas of necrosis (N) and a fibrinous exudate (E) on the serosal surface. Hematoxylin and eosin stain. (Courtesy of MSR Hutt.)

reticuloendothelial system are concentrated (i.e. the spleen, bone marrow, liver and Peyer's patches). In the liver they multiply in Kupffer cells. From the reticuloendothelial system the bacteria reinvade the blood to reach other organs (e.g. kidney). The gallbladder is infected either from the blood or from the liver via the biliary tract, the bacterium being particularly resistant to bile. As a result *S. typhi* enters the intestine for a second time in much larger numbers than on the primary encounter and causes a strong inflammatory response in Peyer's patches leading to ulceration, with the danger of intestinal perforation.

Rose spots on the upper abdomen are characteristic, but absent in up to 50% of patients with enteric fever

After an incubation period of 10–14 days (range 7–21 days), the disease has an insidious onset with non-specific symptoms of fever and malaise accompanied by aches and respiratory symptoms, and may resemble a flu-like illness (see Chapter 10). Diarrhea may be present, but constipation is just as likely. At this stage the patient often presents with a pyrexia of unknown origin (PUO; see Chapter 27). In the absence of treatment the fever increases and the patient becomes acutely ill. Rose spots – erythematous maculopapular lesions that blanch on pressure (*Fig. 20.44*) – are characteristic on the upper abdomen, but may be absent in up to 50% of patients. They are transient and disappear within hours to days. Without treatment, an uncomplicated infection lasts 4–6 weeks.

Before antibiotics, 12–16% of patients with enteric fever died, usually of complications

The complications can be classified into:

- Those secondary to the local gastrointestinal lesions (e.g. hemorrhage and perforation; *Fig. 20.45*).
- Those associated with toxemia (e.g. myocarditis, hepatic and bone marrow damage).
- Those secondary to a prolonged serious illness.
- Those resulting from multiplication of the organisms in other sites causing meningitis, osteomyelitis or endocarditis.



Fig. 20.44 Rose spots on the skin in typhoid fever. (Courtesy of WE Farrar.)

Before antibiotics became available, 12–16% of patients died, usually of complications occurring in the third or fourth week of the disease. Relapse after an initial recovery was also common.

1–3% of patients with enteric fever become chronic carriers

Patients usually continue to excrete *S. typhi* in the feces for several weeks after recovery and 1–3% become a chronic carrier, which is defined as *S. typhi* excretion in feces or urine for one year after infection. Chronic carriage is more common in women, in older patients and in those with underlying disease of the gallbladder (e.g. stones) or urinary bladder (e.g. schistosomiasis).

Diagnosis of enteric fever depends upon isolating *S. typhi* or *S. paratyphi* using selective media

This cannot be made on clinical grounds alone, although the presence of rose spots in a febrile patient is highly suggestive. Samples of blood, feces and urine should be cultured on selective media. Blood cultures are usually positive during the first two weeks, and feces and urine at 2–4 weeks (see Chapter 14). An antibody response to infection can be detected by an agglutination test (Widal test), but interpretation of the results depends upon a knowledge of the normal antibody titers in the population and whether the patient has been vaccinated. A demonstration of a rising titer between acute and convalescent phase sera is more useful than examination of a single sample. At best the results confirm the microbiologic diagnosis, at worst they are misleading.

Antibiotic treatment should be commenced as soon as enteric fever is diagnosed

Effective antibiotics are chloramphenicol, ampicillin, cotrimoxazole or ciprofloxacin and treatment should continue for at least one week after the temperature has returned to normal. Isolates of *S. typhi* resistant to one or more of the above agents have been reported. Many other agents are active *in vitro*, but do not achieve a clinical cure, presumably because they do not reach the bacteria in their intracellular location.

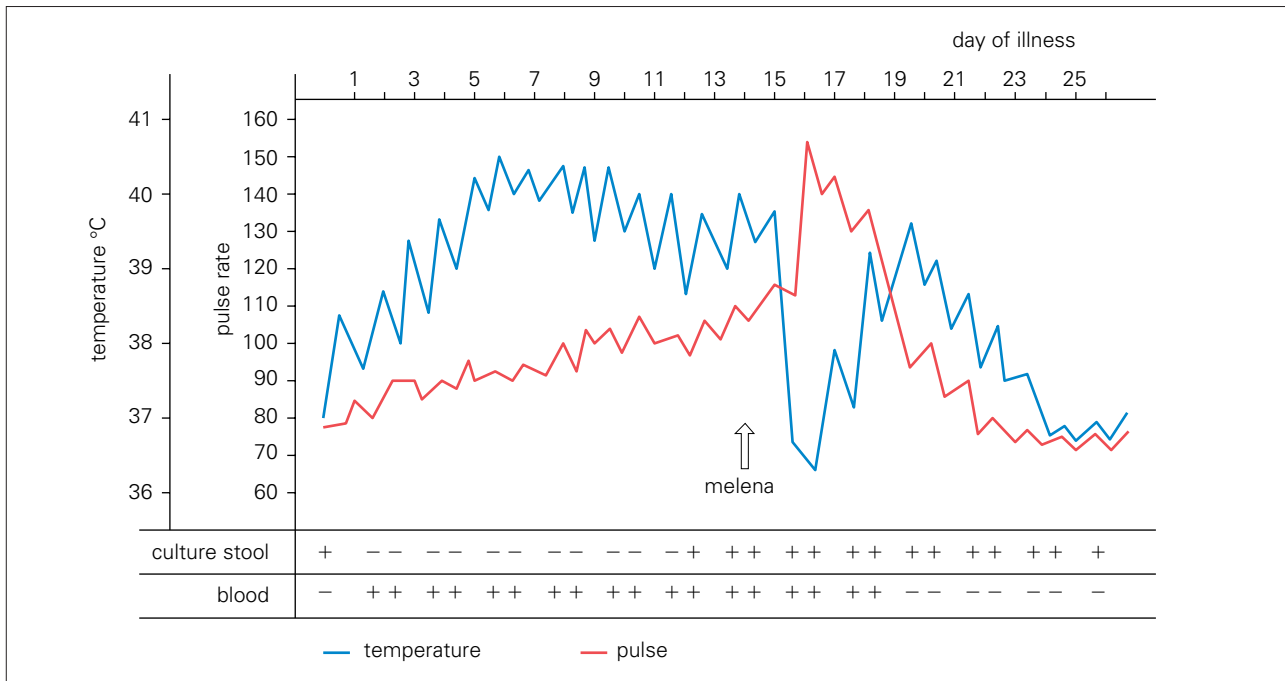


Fig. 20.45 The clinical course of typhoid fever. Chart of temperature, pulse rate and bacteriologic findings in a patient whose illness was complicated by massive hemorrhage. (Courtesy of HL DuPont.)

Prevention of enteric fever involves public health measures, treating carriers and vaccination

Breaking the chain of spread of infection from person to person depends upon good personal hygiene, adequate sewage disposal and a clean water supply. These conditions exist in the developed world where outbreaks of enteric fever are rare, but still occur.

Typhoid carriers are a public health concern and should be excluded from employment involving food handling. Every effort should be made to eradicate carriage by antibiotic treatment and if this is unsuccessful, removal of the gallbladder (the most common site of carriage) should be considered.

A killed vaccine against *S. typhi* and one which includes *S. paratyphi* are available and are recommended for travellers to developing countries; protection, however, is incomplete. Side effects of vaccination include pain at the site of injection, fever and headache. A live oral vaccine (strain Ty 21a) is now available, but protection appears to be short-lived.

Listeriosis

Listeria infection is associated with pregnancy and reduced immunity

Listeria monocytogenes is a Gram-positive coccobacillus that is widespread among animals and in the environment. It is becoming increasingly recognized as a foodborne pathogen, associated particularly with uncooked foods such as pâté, contaminated milk, soft cheeses and coleslaw. It is likely that a large number of organisms must be ingested to cause disease, but the ability of the organism to multiply, albeit slowly,

at refrigeration temperatures allows an infective dose to accumulate in goods stored in this way. Even then, the population at risk appears to be limited to:

- Pregnant women, with the possibility of infection of the baby in the uterus or during birth.
- Immunocompromised people.

The disease usually presents as meningitis (see Chapters 22 and 38).

Hepatitis

There are at least six different hepatitis viruses

Hepatitis means inflammation and damage to the liver, and can be caused by viruses and less commonly bacteria (e.g. *Leptospira* spp.) or other microorganisms. The disease picture varies from malaise, anorexia and nausea to acute life-threatening liver failure, which is rare. More than 50% of the liver must be damaged or destroyed before liver function fails. Regeneration of liver cells is rapid, but fibrous repair, especially when infection persists, can lead to cirrhosis.

At least six different viruses are referred to as hepatitis viruses (Fig. 20.46) and generally they cannot be distinguished clinically. Other viruses cause hepatitis as part of a disease syndrome and are dealt with elsewhere. Dramatic elevations of serum aminotransferase concentration (alanine aminotransferase, ALT; aspartate aminotransferase, AST) are characteristic of acute viral hepatitis. Specific laboratory tests for hepatitis A and B viruses have been available for some years, and tests for others, originally referred to as 'nonA-nonB' viruses are now becoming available. Except in the cases of hepatitis A and B, there are no licensed vaccines, and

VIRAL HEPATITIS								
virus	virus group	type of virus	mode of infection	incubation period	frequency of infection in UK/USA	severity of hepatitis	persistent carriage of virus	other comments
hepatitis A (HAV)	enterovirus 72	ssRNA	fecal-oral	2–4 weeks	++	±	–	common in UK and USA
hepatitis B (HBV)	hepadnavirus	dsDNA	from blood (also sexual)	1–3 months	±	++	+	carriage associated with liver cancer
hepatitis C (HCV)	togavirus	ssRNA	from blood (?also sexual)	2 months	±	+	±	uncommon in UK, USA
hepatitis D (HDV)	very small	ssRNA	from blood	2–12 weeks	±	+	+	needs concurrent hepatitis B virus infection
hepatitis E* (HEV)	calicivirus	ssRNA	fecal-oral	6–8 weeks	–	±	–	common in Far East
yellow fever	togavirus	ssRNA	mosquito	3–6 days	–	++	–	no person-to-person spread

Fig. 20.46 The main viruses causing hepatitis in humans. Other viruses causing hepatitis include Epstein–Barr virus (mild hepatitis in 15% of infected adults and adolescents) and rarely herpes simplex virus, while intrauterine infection with rubella or cytomegalovirus causes hepatitis in the newborn.) *Hepatitis F (HFV) is of uncertain status; hepatitis G (HGV), a flavivirus, is spread via the blood. (ds, double-stranded; ss, single-stranded.)

except for interferons (IFNs; hepatitis B and C) there are no specific treatments.

Hepatitis A

This disease is caused by a typical enterovirus (single-stranded RNA) referred to as hepatitis A virus (HAV) or enterovirus 72. There is only one serotype.

HAV is transmitted by the fecal-oral route

Virus is excreted in large amounts in feces (10^8 infectious doses=g) and spreads from person to person by contact (hands) or by contamination of food or water. The incubation period between infection and illness is 2–4 weeks; virus is present in feces 1–2 weeks before symptoms appear and during the first week (sometimes also the second and third

week) of the illness. Person to person transmission can lead to outbreaks in places such as schools and camps and viral contamination of water or food is a common source of infection (*Fig. 20.47*). In developed countries, 20–50% of adults have been infected and have antibody, whereas in developing countries infection is more common and over 90% of adults have been infected.

Clinically, hepatitis A is milder in young children than in older children and adults

After infection, the virus enters the blood from unknown sites in the gastrointestinal tract, where it may replicate. It then infects liver cells, passing into the biliary tract to reach the intestine and appear in feces (*Fig. 20.48*). Relatively small amounts of virus enter the blood at this stage. Events during



Hepatitis A

In August 1988 the Florida Department of Health and Rehabilitation Services traced 61 people who had suffered serologically-confirmed infection with HAV. These individuals resided in five different states, but 59 of them had eaten raw oysters from the same growing areas in Bay County coastal waters. The oysters had been gathered ille-

gally from outside the approved harvesting areas and were contaminated with HAV. The mean incubation period of the disease was 29 days (range 16–48 days). Probable sources of fecal contamination near the oyster beds included boats with inappropriate sewage disposal systems and discharge from a local sewage treatment plant that contained a high concentration of fecal coliforms.

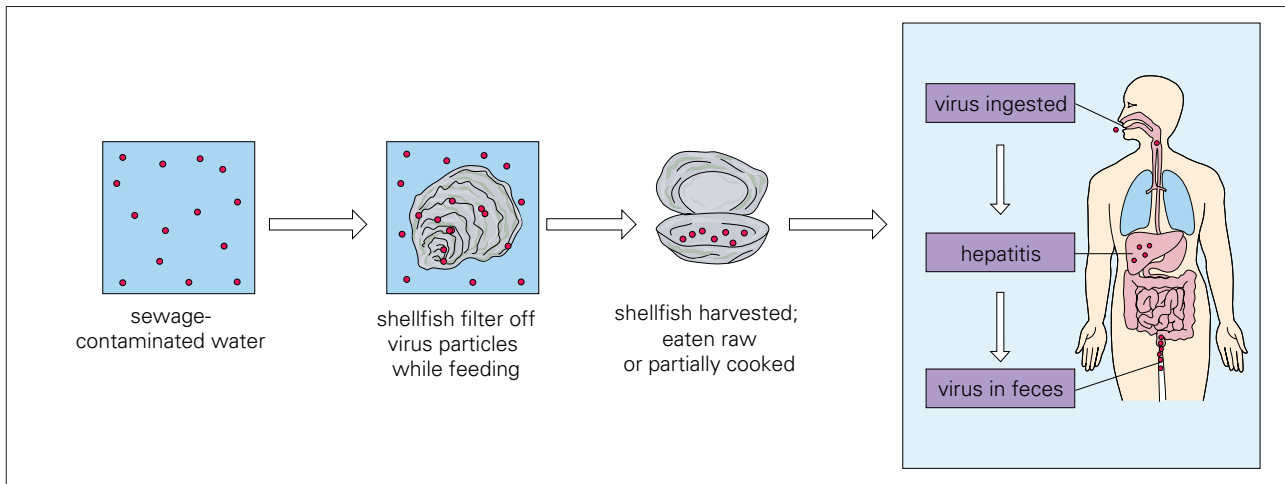


Fig. 20.47 Contamination of shellfish by HAV can lead to human infection.

the rather lengthy incubation period are poorly understood, but liver cells are damaged, possibly by a direct viral action. Common clinical manifestations are fever, anorexia, nausea, vomiting; jaundice is more common in adults. The illness generally has a more sudden onset than hepatitis B.

The best laboratory method for diagnosis is to detect hepatitis A-specific IgM antibody in serum or to demonstrate the antigen in the feces using an ELISA method (see Chapter 14).

Pooled normal immunoglobulin contains antibody to HAV, and gives approximately 1–2 months of protection when injected into travellers to developing countries. There is no antiviral therapy, but an effective formaldehyde-inactivated vaccine is now available.

Hepatitis B

This disease is caused by hepatitis B virus (HBV), a hepadna (hepatitis DNA) virus (see Appendix, and below) containing a partially double-stranded circular DNA genome and

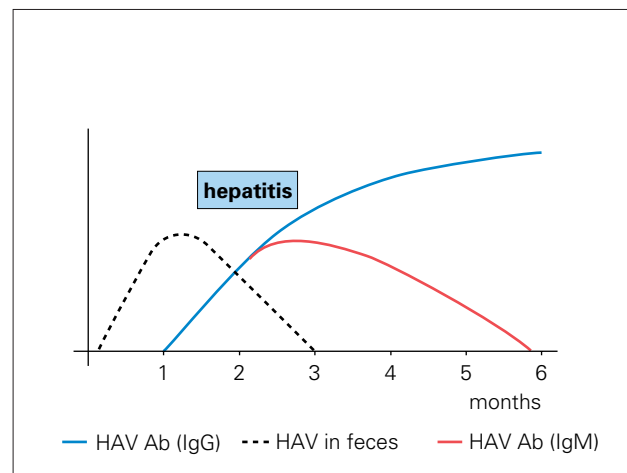


Fig. 20.48 The clinical and virologic course of hepatitis A virus (HAV). (Ab, antibody.)

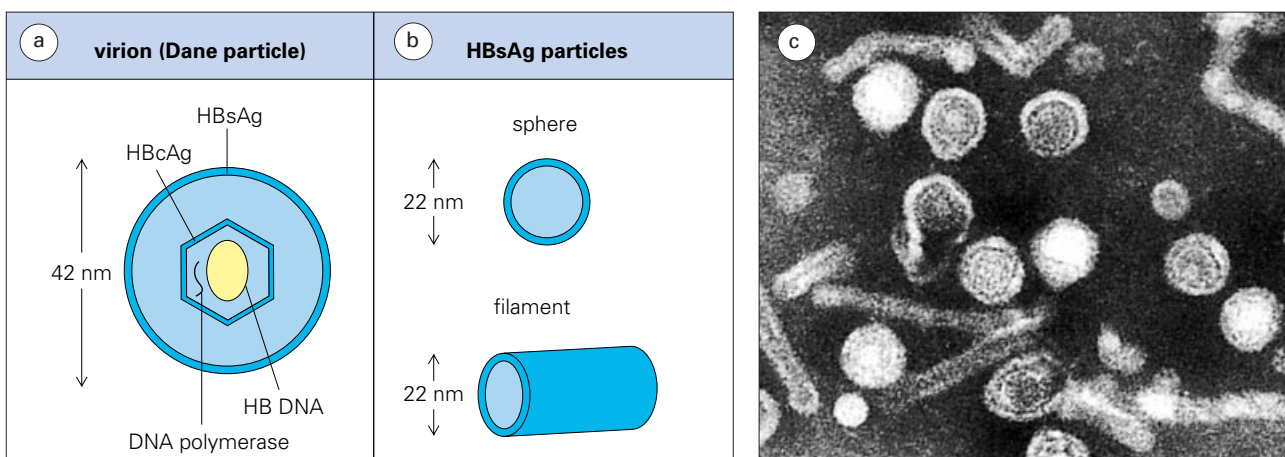


Fig. 20.49 During acute infection and in some carriers there are 10^6 – 10^7 infectious (Dane) particles/ μl of serum (a), and as many as 10^{12} HBsAg particles/ μl (b). (c) Electron micrograph showing Dane particles and HBsAg particles. (Courtesy of JD Almeida.)

three important antigens – HBsAg, HBcAg, and HBeAg (Figs 20.49, 20.50). There is only one serotype in the sense that infection with a given strain of HBV confers resistance to all strains, but antigenic variation in HBsAg gives four subtypes (adw, adr, ayn and ayr). These do not differ in virulence or chronicity, but are useful in epidemiologic studies.

HBV is transmitted in blood

HBV is present in blood and can spread:

- Between intravenous drug misusers or male homosexuals.
- Between mother and child (intrauterine, peri- and post-natal infection; see Chapter 22).
- In association with tattooing, earpiercing and acupuncture.
- Probably heterosexually when there are genital ulcers.

Bloodsucking arthropods do not appear to be important. As blood contains up to one million infectious doses/ μl , invisible amounts of blood can transmit the infection. Virus carriers, of which there are about 350 million worldwide, play a major role in transmission.

HBV is not directly cytopathic for liver cells and the pathology is largely immune-mediated

After entering the body there is probably a preliminary period of virus replication in lymphoid tissue, following which the virus reaches the blood, and then the liver. This results in inflammation and necrosis. Much of the pathology is immune mediated, for instance attack on infected liver cells by virus-specific Tcs. It is not known why the incubation period is so long (1–3 months). As the first virus-specific antibodies are formed there may be a brief prodromal illness with a rash and arthralgia. This is seen in 10–20% of icteric (jaundiced) patients and is due to the formation of immune complexes between HBs and anti-HBs antibody in the circulation in antigen excess (free antibody then being undetectable). These are deposited in the skin and joints for example. (see Chapter 12).

As liver damage increases, clinical signs of hepatitis appear (Fig. 20.51); the disease is generally more severe than hepatitis A. The immune response slowly becomes effective, virus replication is curtailed, and eventually, although sometimes not for many months, the blood becomes non-infectious. The host's

HEPATITIS B ANTIGENS AND ANTIBODIES	
HBsAg	envelope (surface) antigen of HBV particle also occurs as free particle (spheres and filaments) in blood; indicates infectivity of blood
HBsAb	antibody to HBsAg; provides immunity; appears late (not in carriers)
HBcAg	antigen in core of HBV
HBcAb	antibody to HBcAg; appears early
HBeAg	antigen derived from core; indicates transmissibility
HBeAb	antibody to HBeAg; indicates low transmissibility

Fig. 20.50 Characteristics of hepatitis B virus (HBV) antigens (Ag) and antibodies (Ab).

α and β IFN responses to the infection are specifically suppressed by the gene products of this resourceful viral parasite.

Certain groups of people are more likely to become carriers of hepatitis B

About 10% of infected individuals fail to eliminate the virus from the body and become virus carriers. The blood remains infectious, often for life, and although continuing liver damage can cause chronic hepatitis, the damage is often so mild that the carrier remains in good health. Certain groups of people are more or less likely to become carriers as follows:

- People with a more vigorous immune response to the infection clear the virus more rapidly, but tend to suffer a more severe illness.
- Immunodeficient patients develop a milder disease, but are more likely to become carriers.
- There is a marked age-related effect. In Taiwan, for instance, 90–95% of perinatally infected infants became carriers compared with 23% of those infected at 1–3 years of age and only 3% of those infected as university students.
- Sex is another factor, with males being more likely to become carriers than females.

In countries where infection in infancy and childhood is



Hepadnaviruses

Hepadnaviruses are also found in woodchucks, ground squirrels and Pekin ducks. In each case the infection persists in the body, with HBs-like particles in the blood and chronic hepatitis and liver cancer as sequelae. These viruses often infect non-hepatic cells. In northeast USA for

instance, 30% of woodchucks carry their own type of hepadnavirus and most develop liver cancer by later life. The virus replicates not only in liver cells, but also in lymphoid cells in the spleen, peripheral blood and thymus and in pancreatic acinar cells and bile duct epithelium.

common (possibly because there is a high carrier rate in mothers), overall carrier rates are higher. Therefore in West Africa where more than 70% of the population have antibodies, 12–20% of the population are carriers, whereas in western Europe and North America up to 5% of the population have antibodies and 0.9% are carriers.

Complications of hepatitis B are cirrhosis and hepatocellular carcinoma

Complications of hepatitis B include:

- Cirrhosis, as a result of chronic active hepatitis.
- Hepatocellular carcinoma. Hepatitis B carriers are 200-times more likely to develop liver cancer than non-carriers. This is not seen until 20–30 years after the infection. The cancer cells contain multiple integrated copies of HBV DNA (integration takes place in infected liver cells after about two years of carriage) and this could be the carcinogenic factor. Alternatives would be the constant regenerative mitosis of liver cells in response to chronic infection or the presence of an unknown co-carcinogen.

Detection of HBeAg means that there are large amounts of virus in the blood

HBsAg appears in the serum during the incubation period and as the amount increases it signifies that infectious ('Dane') particles are also present (Fig. 20.51). The HBsAg concentration generally falls and finally disappears during

recovery and convalescence, but remains in carriers. As HBsAg disappears, anti-HBs antibody becomes detectable and can be used for diagnosis. Before it becomes detectable, anti-HBc IgM may only be a matter of injection. Anti-HBs is demonstrable in previously infected non-carriers. If HBeAg is detected there are large amounts of virus in the blood and after HBeAg disappears anti-HBe antibody becomes detectable.

Genetically engineered hepatitis B vaccine is safe and effective

There is no standard antiviral therapy. However, large doses of α/β IFN have been used to clear the virus, sometimes permanently, from carriers.

A vaccine is available. Originally it consisted of purified HBsAg prepared from the serum of carriers and wash chemically-treated to kill any contaminating viruses, but the current vaccine is genetically engineered HBsAg produced in yeasts. Two to three injections of vaccine generally give good protection, and vaccination is recommended, especially for those frequently exposed to blood or blood products such as surgeons and other health care workers, dentists, multiply-transfused or dialysed patients, sexual contacts of acute hepatitis B cases, morticians, and intravenous drug misusers. One problem is that up to 10% of normal individuals fail to produce the protective anti-HBs antibody, even when revaccinated. This could be due to genetically determined defects in the

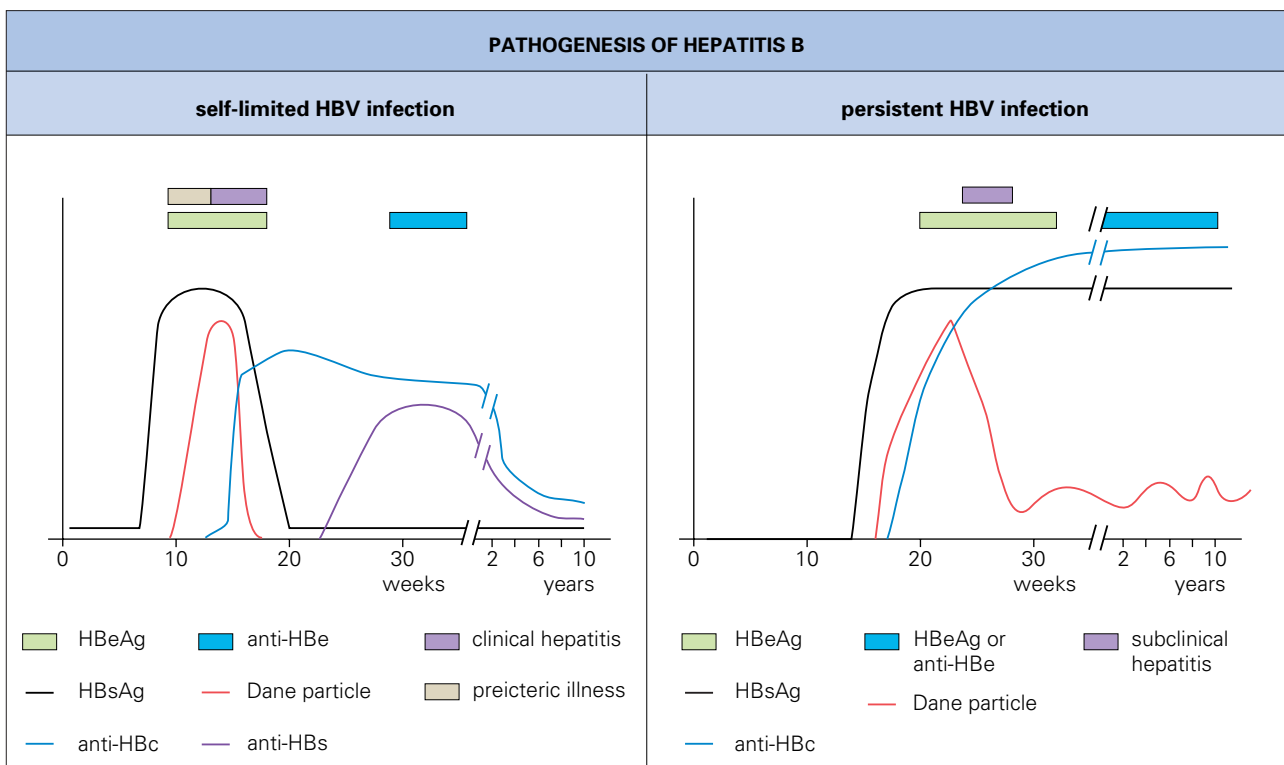


Fig. 20.51 Hepatitis B virus (HBV). (a) Clinical and virologic course of hepatitis B, with recovery.

(b) Clinical and virologic course in a carrier of hepatitis B. Results for HBV DNA polymerase and DNA are not routinely available, but parallel those for HBeAg. (Redrawn from WE Farrar, MJ Wood, JA Innes et al. *Infectious Diseases*, 2nd edition. Mosby International, 1992.)

immune repertoire or because of the induction of immune suppressor cells.

After accidental exposure to infection, hepatitis B immunoglobulin (HBIG) can be used to provide immediate passive protection. This is prepared from the serum of hemophiliacs or others with high titers of antibody to HBs.

In areas of high hepatitis B endemicity such as parts of West Africa, HBIG administered within 24 hours of birth followed by vaccination prevents children of infected mothers becoming carriers.

Hepatitis C

Hepatitis C virus is the commonest cause of transfusion-associated hepatitis

Hepatitis C virus (HCV) was discovered in 1989 as the cause of 90–95% of cases of transfusion-associated nonA-nonB hepatitis. It is a single-stranded RNA virus related to the flaviviruses and pestiviruses. The viral RNA was extracted from blood, a complementary DNA (cDNA) clone was made, and viral protein produced. Antibody to viral protein could then be tested for in sera. The discovery of HCV was a *tour de force* in molecular virology; although it has been cloned it has still not been visualized or grown in the laboratory.

HCV spreads in the same way as hepatitis B

HCV is present in blood (about 10^4 – 10^5 infectious doses/ml), and spreads in the same way as hepatitis B, by blood transfusion, intravenous drug misuse and from mother to infant; sexual transmission is uncommon. There may be other methods of transfer.

About 50% of patients with HCV develop chronic active hepatitis

The incubation period is 2–4 months, at which stage mild disease occurs in about one in 10 individuals. Nothing is known of its pathogenesis. Virus is often detectable in the blood after recovery from the illness, and carriers are a source of infection. In Europe and the USA up to 1% of apparently healthy individuals have antibody and may be infectious. About 50% of patients develop chronic active hepatitis and 20% progress to cirrhosis. Infection is also associated with liver cancer.

If antibody is present it is possible that the virus is also present and the patient is infectious, but this is not necessarily the case. Virus-specific cDNA can be tested for by the polymerase chain reaction.

Results of treatment with IFN α and ribavirin have been encouraging

There is no vaccine. As HCV is now the commonest cause of transfusion-associated hepatitis, blood donors are routinely tested for antibody to hepatitis C.

Hepatitis D

Hepatitis D virus can only multiply in a cell infected with HBV

This is caused by hepatitis D virus (HDV or delta virus), which has a very small circular single-stranded RNA genome and is a defective virus, so-named because it can successfully

multiply in a cell only when the cell is infected with HBV at the same time (see Appendix). When HDV buds from the surface of a liver cell it acquires an envelope consisting of HBs (Fig. 20.52). The HBs envelope makes the 35–37 nm virus particle infectious by attaching it to hepatic cells.

Spread of HDV is similar to that of HBV and HBC

Infected blood contains very large amounts of virus (up to 10^{10} infectious doses/ml in experimentally-infected chimpanzees) and transmission includes heterosexual transmission.

When HDV infection accompanies, or is added to, HBV infection the resulting disease is more severe than with HBV alone. Infection is uncommon in the UK and USA, but common in parts of South America and Africa. Worldwide it is occurs in approximately 5% of HBV carriers.

The laboratory test is for HDAg ('delta' antigen) or antibody to HDAg. HBsAg will be present, although not necessarily at a detectable concentration.

There is no vaccine, but vaccination against hepatitis B prevents infection with hepatitis D.

Hepatitis E

Hepatitis E virus spreads by the fecal-oral route

This disease, also known as enteric nonA-nonB hepatitis, is caused by a small single-stranded RNA virus, probably a calicivirus. The virus is excreted in feces and spreads by the fecal-oral route. Although uncommon in developed countries, it occurs as a waterborne infection in India and may be responsible for 50% of cases of sporadic hepatitis in developing countries. The incubation period is 6–8 weeks. The disease is generally mild, but is severe in pregnant women with a high mortality (up to 20%) involving disseminated intravascular coagulation during the third trimester. The virus is eliminated from the body on recovery and there are no carriers. The possible protective value of passively-administered normal immunoglobulin is being investigated. Serologic tests are also being developed.

Hepatitis F, hepatitis G

Approximately 5–10% of hepatitis cases known to be transmitted by blood transfusion cannot be attributed to a known virus. Perhaps there are even more human hepatitis viruses

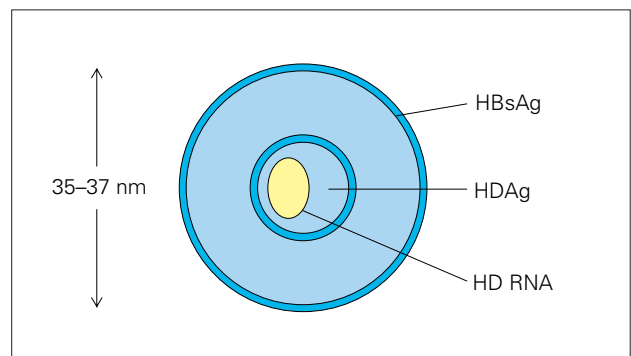


Fig. 20.52 Structure of hepatitis D virus in serum. (Ag, antigen.)

waiting to be discovered. Hepatitis F virus (a virus of uncertain status) and hepatitis G virus (a flavivirus) have been described and cause persistent infection and viremia.

Parasitic infections affecting the liver

An inflammatory response to the eggs of *Schistosoma mansoni* results in severe liver damage

Liver pathology in parasitic infections is most severe in *S. mansoni* infection. Although the worms of *S. mansoni* spend only a relatively short time in the liver before moving to the mesenteric vessels, eggs released by the females can be swept by the bloodstream into the hepatic circulation and be filtered out in the sinusoids. The inflammatory response to these trapped eggs is the primary cause of the complex changes that result in hepatomegaly, fibrosis and the formation of varices (Fig. 20.53).

Whereas schistosomiasis is widespread in tropical and subtropical regions, other parasitic infections affecting the liver

are much more restricted in their distribution (e.g. clonorchiasis, fascioliasis, hydatid disease).

In Asia, infections with the human liver fluke *Clonorchis sinensis* are acquired by eating fish infected with the metacercarial stage. Juvenile flukes released in the intestine move up the bile duct and attach to the duct epithelium, feeding on the cells and blood and tissue fluids. In heavy infections there is a pronounced inflammatory response, and proliferation and hyperplasia of the biliary epithelium, cholangitis, jaundice and liver enlargement are possible consequences. There may be an association with cholangiocarcinoma, but there is little evidence for this in humans.

A number of animal liver flukes can also establish themselves in humans. These include species of *Opisthorchis* (in Asia and Eastern Europe) and the common liver fluke *Fasciola hepatica*. In general the symptoms associated with these infections are similar to those described for *C. sinensis*. Other parasitic infections associated with liver pathology are malaria, leishmaniasis, extraintestinal amebiasis, hydatid disease and ascariasis.

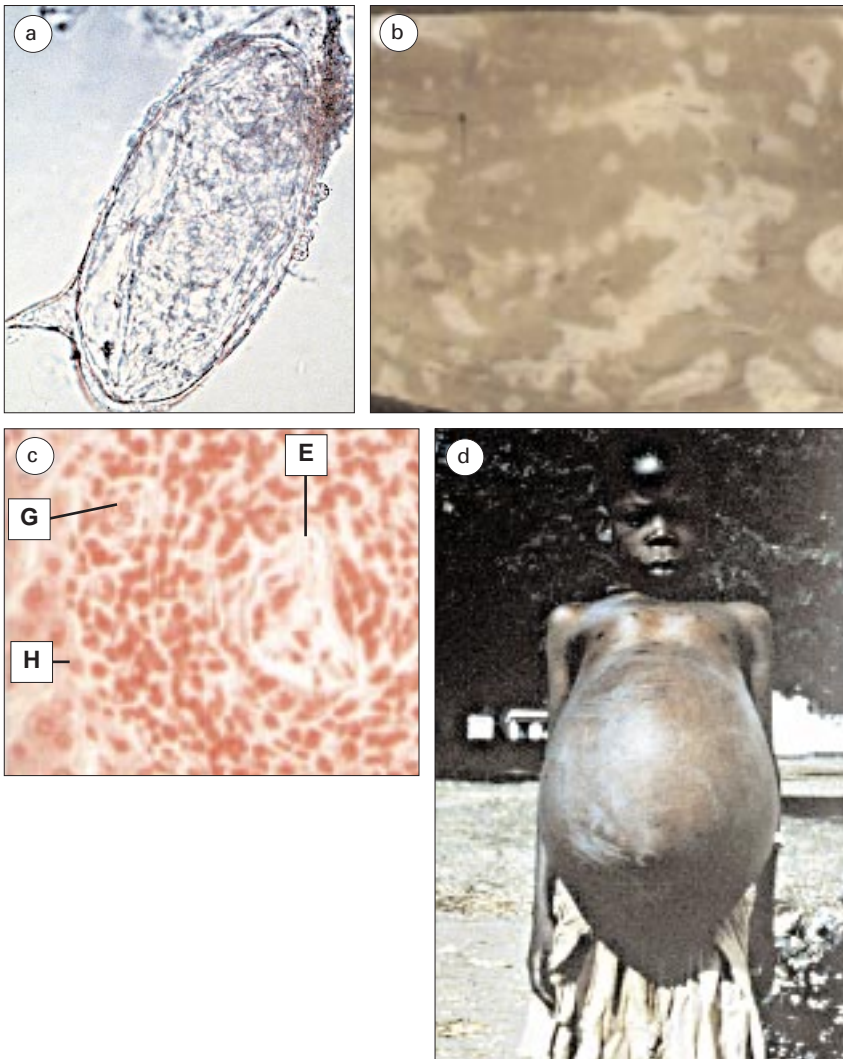


Fig. 20.53 The portal cirrhosis of *Schistosoma mansoni* is the end result of huge numbers of granulomas formed around worm eggs deposited in the liver. In the related *Schistosoma haematobium* infection, a similar process occurs in the wall of the bladder. (a) Egg of *S. mansoni*. $\times 400$. (Courtesy of R Muller.) (b) Pipe-stem cirrhosis in the liver as a result of coalescent calcified granulomas. (Courtesy of R Muller.) (c) Cellular reaction around an egg in the liver. E, egg containing miracidium; G, giant cell; H, hepatic cell. (Courtesy of R Muller.) (d) Clinical schistosomiasis with massive hepatosplenomegaly and ascites due to portal obstruction. (Courtesy of G Webbe.)

Liver abscesses

Despite its name an amebic liver abscess does not consist of pus

E. histolytica can escape from the gastrointestinal tract and cause disease in other sites, including the liver (see above). However, the term ‘amebic liver abscess’ is not strictly accurate because the lesion formed in the liver consists of necrotic liver tissue rather than pus. True liver abscesses – walled-off lesions containing organisms and dead or dying polymorphs (pus) – are frequently polymicrobial, containing a mixed flora of aerobic and anaerobic bacteria (Fig. 20.54). Lesions caused by *Echinococcus granulosus* in hydatid disease can become secondarily infected with bacteria. The source of infection may be local to the lesion or another body site, but is usually undiagnosed. Broad spectrum antimicrobial therapy is required to cover both aerobes and anaerobes.

Biliary tract infections

Infection is a common complication of biliary tract disease

Although infection is not often the primary cause of disease in the biliary tract, it is a common complication. Many patients with gallstones obstructing the biliary system develop infective complications caused by organisms from the normal gastrointestinal flora such as enterobacteria and anaerobes. Local infection can result in cholangitis and subsequent liver abscesses or invade the bloodstream to cause septicemia and generalized infection. Removing the underlying obstruction in the biliary tree is a prerequisite to successful therapy. Antibacterial therapy is usually broad-spectrum, covering both aerobes and anaerobes.

Peritonitis and intra-abdominal sepsis

The peritoneal cavity is normally sterile, but is in constant danger of becoming contaminated by bacteria discharged through perforations in the gut wall arising from trauma (accidental or surgical) or infection. The outcome of peritoneal contamination depends upon the volume of the inoculum (1 ml of gut contents contains many millions of microorganisms), and the ability of the local defenses to wall off and destroy the microorganisms.

Peritonitis is usually caused by *Bacteroides fragilis* mixed with facultative anaerobes

Although the gut contains an enormous range of different bacterial species, peritonitis and intra-abdominal abscesses are usually caused by only a few, primarily strict, anaerobes of the *Bacteroides fragilis* group mixed with facultative anaerobes such as *E. coli*. It is unusual to find a single species causing the infection. *Mycobacterium tuberculosis* and *Actinomyces* can also cause intraperitoneal infection (Fig. 20.55).

Peritonitis usually begins as an acute inflammation in the abdomen and progresses to the formation of localized intra-abdominal abscesses. In the absence of appropriate antibiotic therapy the infection is frequently fatal and even with appropriate treatment, the mortality remains at 1–5%. Antibiotic therapy must be chosen to cover both aerobic and anaerobic pathogens. Suitable regimens include a combination of gentamicin (for the aerobic Gram-negative rods), ampicillin (for

enterococci) and metronidazole (to cover the anaerobes). Mycobacterial infection requires specific antituberculous therapy (see Chapter 30), while actinomycosis responds well to prolonged treatment with penicillin.

Summary

The length and complexity of the gastrointestinal tract is matched by the variety of microorganisms that can be acquired by this route, causing damage locally or invading to cause disseminated disease. Diarrheal disease is a major cause of morbidity and mortality in malnourished populations in the developing world and will only be combatted successfully when there are adequate public health measures. Meanwhile in the developed world, diarrheal disease is still common and causes severe illness in the very young and the very old. Certain infections such as typhoid are initiated in the gastrointestinal tract, but cause systemic disease, while hepatitis A is acquired and excreted by the intestinal route. The remaining members of the hepatitis ‘alphabet’ are also dealt with in this chapter. Infections result not only from the ingestion of pathogens from an external source, but also from the normal flora of the gastrointestinal tract if there are accidental or manmade breaches of the mucosa as microorganisms can then ‘escape’ and cause intra-abdominal sepsis.

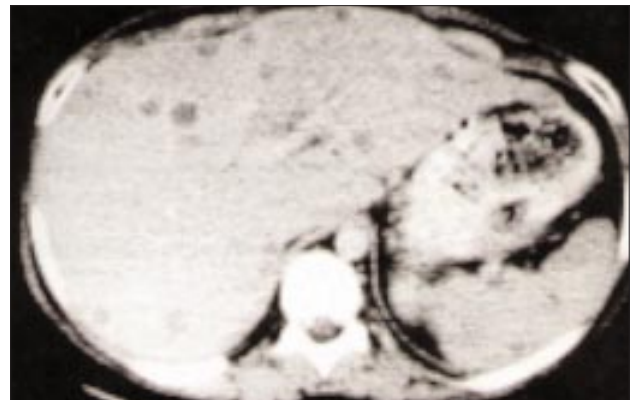


Fig. 20.54 Multiple pyogenic liver abscesses due to *Pseudomonas aeruginosa*. (Courtesy of N Holland.)



Fig. 20.55 Tuberculous peritonitis. Edematous bowel with multiple lesions on the peritoneal surface. (Courtesy of M Goldman.)



- Diarrheal disease is a major cause of morbidity and mortality in the developing world. A wide range of diverse microbes cause infections of the gastrointestinal tract. Diarrhea, the most common symptom, ranges from mild and self-limiting to severe with consequent dehydration and death.
- Gastrointestinal pathogens are transmitted by the fecal–oral route. They may invade the gut, causing systemic disease (e.g. typhoid), or multiply and produce locally acting toxins and damage only the gastrointestinal tract (e.g. cholera). The number of organisms ingested and their virulence attributes are critical factors determining whether infection becomes established.
- Microbiologic diagnosis is usually impossible without laboratory investigations, but the patient's history, including food and travel history, provides useful pointers.
- The major bacterial causes of diarrhea are *E. coli*, salmonellae, *Campylobacter*, *V. cholerae* and shigellae. Other less common causes include *Cl. perfringens*, *B. cereus*, *V. parahaemolyticus* and *Y. enterocolitica*. Food poisoning (i.e. the ingestion of bacterial toxins in food) is caused by *Staph. aureus* and *Cl. botulinum*.
- *E. coli* is the major bacterial cause of diarrhea in developing countries and of traveller's diarrhea. Distinct groups within the species (ETEC, EHEC, EPEC and EIEC) have different pathogenic mechanisms – some are invasive, others toxigenic.
- Salmonellae and *Campylobacter* are common in the developed world, have large animal reservoirs and spread via the food chain. Both cause disease by multiplication in the gut and the production of locally acting toxins.
- *V. cholerae* and shigellae have no animal reservoirs and the diseases are potentially eradicable. Transmission is prevented by good hygiene, clean drinking water and hygienic disposal of feces. The pathogenesis of cholera depends upon production of cholera enterotoxin, which acts on the gastrointestinal mucosal cells. In contrast, *Shigella* invades the mucosa, causing ulceration and bloody diarrhea, symptoms similar to those of amebic dysentery.
- *H. pylori* is associated with gastritis and duodenal ulcers. Removal of the bacterium by combination treatment with antibiotics and proton pump inhibitors reduces symptoms and encourages healing.
- Disruption of the normal bacterial flora of the gut (usually due to antibiotic treatment) allows organisms normally absent or present in small numbers (e.g. *Cl. difficile*) to multiply and cause antibiotic-associated diarrhea.
- Viral gastroenteritis causes appalling morbidity and mortality, especially in young children in the developing world. The chief culprits are the rotaviruses, which are specific to humans, spread by the fecal–oral route and restrict their multiplication to the gastrointestinal epithelial cells, which they destroy. Very small numbers can initiate infection and multiply in the gut to produce enormous numbers for excretion and transmission to new hosts.
- Ingestion of food or water contaminated with *S. typhi* or *S. paratyphi* can result in the systemic infection enteric (typhoid) fever. These pathogens invade the gut mucosa and are ingested by, and survive in, macrophages. They are transported via the lymphatics to the bloodstream from whence they seed many organs and give the characteristic multisystem disease. Positive diagnosis depends upon culture of the organism. Specific antibiotic therapy is required and specific prevention is achievable through immunization.
- Hepatitis is usually caused by viruses and there are at least six different types (hepatitis A–G), from different virus groups. Hepatitis A and E are transmitted by the fecal–oral route and the rest by contaminated blood or the sexual route. Infection with HBV and HBC often leads to chronic hepatitis or liver cancer.
- Many protozoa and worms live in the intestine, but relatively few cause severe diarrhea. Important protozoa are *E. histolytica*, *G. lamblia* and *Cryptosporidium*, which are acquired by ingestion of infective stages in fecally contaminated food or water. Important worms are *Ascaris*, *Trichuris* and the hookworms. They have more complex routes of transmission with the eggs or larvae requiring a development period outside the human host.
- Parasitic infections involving the liver include infections by *S. mansoni* in the tropics and subtropics, and *C. sinensis*, the human liver fluke, in Asia. Other parasitic infections with important liver pathology include malaria, leishmaniasis, extraintestinal amebiasis, hydatid disease and ascariasis.
- Infection of the biliary tree is usually secondary to obstruction. The normal intestinal flora cause mixed infections, which may extend to produce liver abscesses and septicemia.
- Peritonitis and intra-abdominal sepsis follow contamination of the normally sterile abdominal cavity with intestinal microbes. The presentation is acute and infection can be fatal. Antibiotic therapy against both aerobic and anaerobic bacteria is essential.



A 24-year-old astrologer with a history of intravenous drug abuse sees his doctor because he has felt tired and unwell for the past few weeks. He has noticed that his urine is very dark, he feels nauseated, and does not feel like eating, and he has developed right-sided abdominal discomfort. A friend thinks that he looks 'yellow'. On examination he is tattooed, has yellow sclerae, and is tender in the right upper quadrant of his abdomen. His liver is enlarged, firm and smooth.

The results of investigations including the liver function tests are: AST, 1200 IU/l; ALT, 1000 IU/l; ALP, 100 IU/l; bilirubin, 60 μ mol/l.)

1. What is the most likely diagnosis and what is the differential diagnosis of a viral hepatitis in this setting?
2. What investigations would you perform?
3. How would you manage this man?
4. What other factors are important regarding the control of infection?



In September 1994, 80 cases of *F. S. enteritidis* gastroenteritis were reported from Minnesota, USA, plus 14 cases from South Dakota and 48 from Wisconsin. All had eaten a certain brand of nation-wide distributed ice-cream. The outbreak caused an estimated total of 2000 cases of illness in 41 different states (MMWR 1994; 43:740–741.)

1. Why was ice-cream involved and where did the bacteria come from?
2. What treatment would you have recommended for the patients?
3. What actions would you have recommended in the ice-cream plant?



An 11-month-old baby girl is admitted to the pediatric unit with a two-day history of fever, vomiting, and copious watery diarrhea. She was a full-term normal delivery and has two siblings, one of whom had a mild diarrheal illness that cleared up four days earlier.

On examination she is unwell, mildly dehydrated, and febrile with a temperature of 38°C. Her abdomen is soft and there are no other findings of note.

1. What would be your immediate management of this baby?
2. What viral causes of diarrhoea are most likely?
3. How would a viral infection be diagnosed?
4. What is the natural course of the infection?

Further Reading

Blacklow NR, Greenberg HB. Viral gastroenteritis. *New Engl J Med* 1991;**325**:252–264.

Farrar WE, Wood MJ, Innes JA *et al.* Infectious Diseases, 2nd edition. London: Mosby International, 1992.

Field M, Rao MC, Chang FB. Intestinal electrolyte transport and diarrheal disease. *N Engl J Med* 1989;**321**:800–806.

Gross RJ. The pathogenesis of *Escherichia coli* diarrhoea. *Rev Med Microbiol* 1991;**2**:37–44.

Lemon SM. Type A viral hepatitis: new developments in an old disease. *N Engl J Med* 1985;**313**:1059–1067.

McMahon BL, Alward WLM, Hall DB *et al.* Acute hepatitis B infection: relation of age to the clinical expression of disease and subsequent development of the carrier state. *J Infect Dis* 1985;**151**: 599–603.

Moayyedi P, Anthony TR. *Helicobacter pylori*: the research explosion. *Curr Opin Infect Dis* 1995;**8**:374–379.

Nair GB, Albert MJ, Shimada T *et al.* *Vibrio cholerae* O139 Bengal: the new serogroup causing cholera. *Rev Med Microbiol* 1996;**7**:43–51.

World Health Organization. *Readings on Diarrhoea. Student Manual.* (WHO/CDD/SER/90,13) Geneva: World Health Organization, 1990.

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